THE MEDICAL CLINICS
OF
NORTH AMERICA

Volume 14 Number 2

CLINIC OF DR. CHARLES A. DOAN

FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, NEW YORK

THE NEWER AIDS TO DIAGNOSIS AND PROGNOSIS IN TUBERCULOSIS

WHILE the finding of tubercle bacilli in suspected tuberculous disease will probably always remain for the clinician the most desirable confirmation of his diagnosis, the difficulties attending the realization of this ideal in practice have proved a constant stimulus to investigators toward the development of dependable substitutes. The same is even more true of prognostic data, where even the finding of acid-fast organisms may contribute nothing toward the knowledge of the extent and course of the infection.

For these reasons, and because of the mystery still surrounding the fundamental mechanism of the disease itself—the biological and serological interactions between host and bacterial parasite within the body—the National Tuberculosis Association, under its Research Committee, has undertaken to direct during recent years an intensive study of the chemistry and biology of the entire acid-fast group of micro-organisms. It has enlisted in this undertaking workers in the fundamental sciences of bacteriology, chemistry, and biology, and clinicians, as well as the bacteriological departments of large pharmaceutical houses. These investigators are scattered in some twenty-one different laboratories and institutions throughout this country,[1] their individual attack being correlated and integrated toward

the common goal of all, to the end that advantage may be taken more quickly of new evidence and material originating in any one place. Also the definite interdependence of certain groups separated widely from a geographical and technical standpoint makes the cooperation absolutely essential to attain the necessary ends.

THE VALUE OF THE PERIPHERAL BLOOD COUNT

A resurvey with improved technic of certain previously well-traversed fields has yielded data of considerable interest and significance. The study of the cellular changes occurring in the peripheral blood during the course of experimental tuberculosis has elicited certain new facts which, in turn, have been related to the progress or regression of the lesions within the organs and tissues. These interpretations have been made possible through the application by Sabin[2] of the supravital technic to blood, and later to tissue cells, which has permitted a more certain differentiation of the mononuclear cells of the blood into monocytes and lymphocytes. Vital neutral red, when applied *in vitro* in physiologic concentration to the living cells of the blood, reveals a structure of small vacuoles in the monocyte centered about the centrosome, which does not appear in the fixed cells stained with the usual Romanowsky blood stains. The lymphocytes ordinarily react only with Janus green with accentuation of the mitochondria; the occasional small vacuole taking the neutral red does not confuse the lymphocyte with the monocyte.

It was this rosette of neutral red staining bodies found as a distinguishing characteristic of the blood monocyte which led to an identification of the relationship existing between the monocyte of blood and normal tissues and the epithelioid cell in tuberculosis.[3] The epithelioid cell of the tubercle shows a large, pericentrosomal rosette which reacts with neutral red and occupies the cytoplasm in the hof of the nucleus. Moreover, the typical giant cell of the tubercle, the so-called "Langhans' giant cell," has a similar large rosette of very fine bodies staining with neutral red, which become so dense in the center of the cell

that the nuclei are forced to the periphery, thus making the characteristic by which these giant cells have been distinguished. In such studies it has been determined that the monocyte is the cell from which develop the mononuclear epithelioid cell with accentuated rosette and the multinucleated epithelioid or Langhans' giant cell in tuberculous disease.

When it is recognized that the relative and absolute numbers of lymphocytes and monocytes as found in the peripheral blood are as accurate an index of lymph node and connective tissue activity respectively, as are the granulocytes, platelets, and red cells of the activity of bone marrow, then only will it be understood that interpretations may be made and conclusions drawn from their relationships which have been neglected and overlooked by the clinician in the past. When new rosette cells of the monocytic series are developed in the organs and tissues as a part of the reaction to the tubercle bacillus, this increase is reflected in the circulating blood.[4, 5] A reciprocal fall in lymphocytes accompanies the rise in monocytes. The converse is true in the presence of healing or receding lesions; therefore, the importance of differentiating between the so-called "mononuclear cells" of the blood.

The history of the type of cell now discriminated as the monocyte of the blood, distinct on the one hand from the granulocyte and on the other from the lymphocyte, is a confused one. The monocyte was first considered in the Ehrlich classification as a *transitional* form in the maturation of the neutrophilic leukocyte. The correction came with the introduction of the Romanowsky methylene blue-azure staining technic, showing that the lymphocyte and monocyte both contained azure granules, and Pappenheim and Ferrata fully demonstrated, in 1911, the independence of monocyte and granulocyte. But this tended to link monocyte and lymphocyte until it was seen that the azure granules of lymphocytes are large, few in number, and inconstant in a clear cytoplasm, while the azurophilic granules of the human monocyte are tiny and usually extremely numerous, embedded in a dense, muddy blue background. The monocyte was definitely described as making a third strain of the white cells of the blood,

distinct from granulocytes and lymphocytes, by Schilling-Torgau in 1912, and since that time this interpretation has been generally recognized and accepted by hematologists.

The more recent association of the blood monocyte with the connective tissues, marking its origin and function as primarily there, has again threatened its birthright. The whole experience with tissue culture up to the present time has tended to strengthen the position that monocyte and clasmatocyte are but different phases in the life history of one strain of cells, the connective tissue macrophage. It cannot, however, be controverted that there are two morphological entities in blood and connective tissues, for which two names must be retained for descriptive purposes at least. This is best demonstrated with the supravital technic, in which the monocyte reacts to the neutral red with a rosette of small bodies staining a characteristic salmon pink and arranged about the centrosphere in the hof of the nucleus. These structures, which are not identical with the azurophilic granules stained with the Romanowsky dyes, appear first as do the granules of the myelocyte, in a primitive basophilic cell, the monoblast, which passes through a developmental period before maturity. Unlike other definitive blood cells, the circulating monocyte retains the power of division, and is not infrequently found in mitosis in the blood. The clasmatocyte, in contradistinction, is usually a larger cell without apparent maturation phase, with no cytoplasmic pattern, more highly phagocytic and with its vacuoles reacting to the neutral red in a range from yellow to deep maroon. Contrast, for instance, Kupffer cell or tissue macrophage and blood monocyte. The question must, nevertheless, remain open at the present time as to whether the young rosette cell, however markedly individual morphologically, is normally a definitive cell, or whether it is the stem cell from which under differing conditions evolves, on the one hand, the epithelioid type and, on the other, the typical highly phagocytic clasmatocyte.

Two other desiderata with reference to these cellular differentiations may be mentioned. First, with reference to the motility as seen in studies of the living cells, both monocytes and

clasmatocytes have a delicate, constantly waving, surface film as a part of their mechanism adapted to phagocytic function. The motility of the lymphocyte is inherent in the nucleus with a passive part played by the cytoplasm. The ameba-like pseudopodia and streaming of the granules in the myeloid elements provide the well-known means of progressive movement in this group of cells. Second, all of the recent studies of the tubercle by the newer methods, whether in the actual disease or in the chemically produced tubercular tissue, strengthen Baumgarten's original concept of the origin of this pathologic structure from cells of the connective tissues. The demonstration of the direct origin, as an intervascular element, of the epithelioid cell from the monocyte which in turn derives from a reticular rest, divorces the endothelium of the vascular bed from any part in their development.

The literature, particularly the clinical, reflecting this uncertainty of classification, has continued, even to the present time, to give records of blood counts in which monocytes, clasmatocytes, and lymphocytes are recorded as mononuclear cells without differentiation. The confusion attendant upon the failure to recognize these cell differences, as well as the lack of legitimate diagnostic help to be expected from a differential blood count, may well be illustrated in four different disease entities: in undulant fever there may be quantitative and characteristic qualitative changes in the monocytes of the blood; infectious mononucleosis shows a mononuclear increase which is lymphocytic rather than monocytic in nature; in lobar pneumonia, the neutrophil leukocytosis, which dominates until crisis, is followed by a transitory rise of monocytes (two to three days) and then the postinfective lymphocytosis if resolution is uneventful; if resolution is not progressing or empyema threatens, the monocytes remain high as a warning (Hickling); in tuberculosis it is the monocyte-lymphocyte ratio which is significant in following the progress of the case. It is therefore evident that any aid which is to be expected from studies of the cells of the peripheral blood must be predicated upon the most careful differential counting of all the white blood cells.

Two other points need emphasis. Qualitative changes, particularly in the monocytes, best recognized and detected in the supravital preparations of living cells, are quite as significant as quantitative changes. The appearance of epithelioid cells in the circulating blood of a patient, has been recorded before the finding of other definite diagnostic data, and where tubercle bacilli were subsequently isolated. Characteristic changes in the monocytes toward the epithelioid type are almost equally significant. Then, it is obvious that the value of data, such as are afforded by blood cell differentials, increases in direct proportion to the number of observations. A single determination may not be depended upon, except in rare instances, as indicated above. Rather it is the quantitative trend, as noted in a gradually increasing or decreasing monocyte-lymphocyte ratio over a period of time, which forms the basis for prognosis. A gradually increasing volume of clinical confirmation from studies of tuberculosis in children and adults[6, 7, 8, 9, 10] is substantiating the significance and sensitiveness of the M/L index as a guide in the following of the individual case.

Medlar[11] has pointed again recently to the necessity for evaluating the blood picture in tuberculosis as a whole, indicating the importance at times of the neutrophilic leukocyte. Certainly no one group or combination of cells can alone give the whole cellular story of tuberculosis, but the ease with which non-tuberculous stimuli may elicit fluctuations in the granular cells from the marrow, at least, suggests great caution in relating to this chronic disease every change in this group of blood cells. On the other hand, the "septic picture" with granulocytes at a maintained level above normal has preceded cavitation and spread of the disease very frequently, and there is basis in the pathologic changes involved for such a finding. Medlar believes, as do many of us, that the changes which occur in the cells of the blood in tuberculosis, when properly studied and followed, provide a more sensitive index of what the future holds in store for the individual case than physical signs or *x*-ray films.

Is the blood an *index* of resistance or are the changes in the relative and absolute numbers of the different cell types really

intimately a part of a changing immunity reaction? Is the monocyte a liability or an asset to the body in the presence of tubercle bacilli? That the intact bacilli are always to be found within the epithelioid cells in the disease, and that they may multiply and grow within these cells in tissue culture (Maximow) suggest that they may not be a defensive mechanism. Moreover, the vague shadows in chest plates, representative of a "spread," are epithelioid cells invading surrounding tissues, much as tumor cells invade, and only after the limiting capsule of lymphocytes has circumscribed and sharply delimited the lesion does organization and regression occur. And whether this series of events will occur may often be predicted by the number of lymphocytes relative to monocytes found in the peripheral blood. Should there be 2000 monocytes per cubic millimeter in each of 2 cases, indicating in each instance some activity with a spread of tuberculous foci, the prognosis would be entirely different, depending upon whether the lymphocytes were 2000 or 7000 per cubic millimeter. In brief, the tubercle, always classically interpreted as the manifestation of an immunity reaction, probably is an evidence of resistance only when, and in so long as, the lymphocytic capsule effectively limits the spread of the central core of epithelioid cells within which are living tubercle bacilli. A freely wandering epithelioid cell containing tubercle bacilli is probably potentially as dangerous from the standpoint of the establishment of a metastatic focus as would be a malignant tumor cell under similar circumstances. With a reserve of lymphocytes, as indicated by a high level in the blood stream, making a relatively low M/L index, encapsulation seems to occur more readily with a corresponding limitation to the dangerous extension of the disease.

Certain experimental studies have given further support to this interpretation of the significance of the M/L index to primary cellular resistance in tuberculosis. Rabbits with a high M/L index, *i. e.*, monocytes approaching in relative number the lymphocytes, die more quickly, and animals with a low M/L index survive for considerably longer periods than those with the average M/L index of 0.300, after a given dose of a culture

of bovine tubercle bacilli of known virulence. If rabbits with an average M/L index are given, by special experimental procedures,[12] a higher or a lower index, their anticipated resistance to the same given dose of organisms can be altered, as shown by a shorter or longer survival period respectively.

Thus not only may the monocyte-lymphocyte ratio be an index of the state of activity of the disease in a case of tuberculosis already established, but, on the basis of the experimental studies here indicated, it may also be taken as a measure of susceptibility to primary infection. Further studies are in progress to test more extensively this hypothesis.

RECENT CHEMICO-BIOLOGICAL STUDIES

Of the biological studies thus far made on the basis of the comprehensive, large scale, chemical analysis of organisms and media undertaken by the Sterling Chemistry Laboratory, Yale University, and by the Pathological Department of Chicago University, those with the lipoids have been carried farthest. The chemistry of the sugars and proteins as now being studied by Drs. Long and Seibert, Chicago, Dr. Heidelberger, Columbia, and Dr. Johnson and his associates at Yale gives promise of results with important, practical, clinical application in the very near future.

Preliminary biological studies in this laboratory with the chemical fractions thus far available have indicated that the cellular manifestations peculiar to tuberculosis receive their stimulus from the lipoids of the bacillus. Dr. R. J. Anderson and his associates at the Sterling Chemistry Laboratory, Yale University, have partitioned the lipoids from human, avian, bovine, and the nonpathogenic timothy acid-fast organisms. The "phosphatide" fraction,[13] when given into the tissues, produces a sterile reaction indistinguishable otherwise from that seen in the disease.[14] Epithelioid cells and epithelioid or Langhans' giant cells develop with lymphocytic infiltrations, and if the animal is permitted to survive, regress without at any time causing embarrassment to the animal or clinical symptoms or signs. It is impossible to elicit allergic phenomena in animals with this

massive development of tubercular tissue. On the other hand, the protein and polysaccharides produce fever, hemorrhage, toxicity, and in some instances death. Further chemical studies are necessary before a more complete separation of the toxic manifestations attributable to the proteins, as distinguished from those secondary to the specific polysaccharides, may be made. When these reactions are fully understood, the way will be cleared for the development of a purified protein for use in the skin test instead of the Old Tuberculin of variable composition and standard now in use. This will permit valuable quantitative studies in the future, which are at present impossible. The necessity for a close following of the literature in this field in the near future is indicated from the nature and fruitfulness of the investigations now in progress in the various laboratories.

Dr. Anderson has isolated certain liquid, saturated, fatty acids[15] from the phosphatide and from other of the lipoid fractions which have seemed to carry the active principle for epithelioid cells.[16] However, their salts have not proved to be antigenic when injected intravenously at intervals into animals. With the more complex phosphatide, the opposite has been found to be true, viz., that when given in antigenic dosage intravenously, an antibody, apparently specific, is formed, as indicated by precipitin and complement fixation tests and absorption experiments.[17, 18] When individual rabbits show a low titre after intravenous phosphatide, an increase in epithelioid cells in the tissues may be found; conversely, when the serological reaction has been more striking, very little cellular reaction in the tissues is evident. These observations, together with the fact that in experimental tuberculosis either free phosphatide or phosphatide antibody, or both, may be demonstrated in appropriate fluids at certain stages in the disease, form the basis for a precipitin test as an aid to diagnosis when other methods have failed.

A PHOSPHATIDE PRECIPITIN TEST AS POSSIBLE AID TO DIAGNOSIS AND PROGNOSIS IN TUBERCULOUS DISEASE

The difficulty with which acid-fast bacilli are demonstrated in the various body exudates of suspected tuberculous origin—

spinal fluid, pleural effusion, joint fluid, ascites—and the long period usually elapsing before animal inoculation reveals the presence or absence of specific infection are the common experience of all clinical diagnosticians. In our hands the phosphatide fraction A-3, as prepared by Dr. Anderson, and an antibody demonstrable in rabbits after antigenic injections of this material, have frequently given positive evidence of active tuberculosis when applied in a precipitin test to such fluids, including blood serum. Subsequent finding of the bacilli, or *x*-ray or autopsy confirmation of the diagnosis have checked the positive findings in a majority of the 350 cases. Spinal fluid in the absence of tuberculous lesions in the meninges does not react positively, even though tuberculosis exists elsewhere in the body; spinal fluid in meningitis of other etiology has failed to give positive reactions with tuberculophosphatide. In an early stage of tuberculous meningitis, free antigen is frequently found with an antiphosphatide serum, and a low antibody titer with the phosphatide as antigen. In the late anergic stage of tuberculosis, again free antigen may be found present with very low antibody titer.

The variability and difference in degree of the serologic reaction to the tuberculolipoid in individual animals have been mentioned, and correspond to the well-recognized differences observed in animals sensitized with identical dosages of the same protein antigen. It is therefore necessary to use both antigen and antibody for this test to be of greatest value in either diagnosis or prognosis. If no phosphatide antigen is found and low antibody, the lesion might be expected to be quiescent or inactive, or regressing. If antigen is present and low antibody, the prognosis is probably bad, with little resistance being manifested, that is, the body either inherently or otherwise is unable to bind and thus inactivate the metabolic or catabolic products of the tubercle bacilli within the body, which are thereby free to stimulate a proliferative reaction in the organs and tissues. If no antigen be present, but a high antibody titer is registered, active disease is probably present with fair resistance, its relative effectiveness being further estimated from careful studies of the white blood cells. In old healed tuberculosis, but with a

maintained positive intracutaneous skin reaction to Old Tuberculin, the precipitin test, as performed on the blood serum, has not been positive in the active range.

Thus, at least in selected cases, we have found the precipitin test of value both diagnostically and prognostically. A larger clinical experience must establish its reliability or fallibility as a test which will differentiate and reflect the nature and progress of tuberculous infection.

THE IMPLICATIONS OF THE NEWER BACTERIOLOGICAL STUDIES

The development by Petroff[19] of a method for culturing acid-fast organisms on plates in single colonies has revolutionized our concepts of the bacteriology of this group. Quite aside from the marked differences in colony structure, chromogenic properties, physical and tinctorial characteristics demonstrated within supposed pure strains of organisms by Petroff and his associates of the Trudeau Laboratory, it provides opportunity for virulence studies on the progeny of single organisms as developed in the colony arising from one isolated bacillus. For the first time biological studies may be made with tubercle bacilli on the same basis as those employed in the more rapidly growing pyogenic group, where the single colony in pure cultures has always formed the point of departure for all studies.

It has been found that differences in virulence attend the differences in colony development and bacterial structure. The "S" colonies of avian and bovine tubercle bacilli are smooth, moth ball-like, moist, easily emulsified in an even suspension, and made up of small, pleomorphic, faintly acid-fast organisms of marked virulence. The "R" colonies are rough, dry, granular, impossible to emulsify or free of flocculi, and morphologically show the typical clumping of long, beaded, strongly acid-fast, branching bacilli, with less virulence. The human organism, while showing differences in colony structure and virulence largely differentiated and maintained by subculturing on buffered media at slightly different hydrogen ion concentrations, does not show the smoothness and roughness of colonies in the same degree as the two other types. The difference is rather in delicacy of

growth and lack of chromogenicity on the part of the more virulent organisms as contrasted with a coarse chromogenic pellicle of less virulence when a slightly acid *p*H is maintained (Petroff).

Two points of importance to the clinician are thus brought forward by Petroff's work. First, it is essential that great care be exercised in staining sputum and other suspected material so as not to overdecolorize and thus lose the small virulent organisms which are not strongly acid-fast. Cooper's modification[20] of the Ziehl-Neelsen stain with the addition of 10 per cent NaCl to the carbolfuchsin and with counterstain of methyl green tends to fix and reveal by contrast all acid-fast organisms present. Second, not only is a Gaffky estimation of the number of bacilli present important, but of equal import is an analysis of the relative percentage of different morphological forms to be found at a given time in a given specimen. Thus, chronicity and relative quiescence are indicated when only small clumps of long, beaded, strongly acid-fast, branching, and angulated forms are found; that is to say, when the "typical" arrangement and morphology of the tubercle bacilli are present. These organisms, upon plating according to Petroff's technic, give a predominant growth of so-called "R" colonies. On the other hand, an abundance of acid-fast granules (Muck granules), or short, faintly acid-fast coccoid bacilli may accompany active, invading or cavitating lesions, and cultures reveal an abundance of "S" colonies. The virulence of the latter colonies has been greater for animals. Petroff has in fact followed individual clinical cases through periods of spread with subsequent subsidence of the acute manifestations, and has found the morphology of the organisms and the percentage of "R" and "S" colonies as plated and counted, changing and heralding the respective pathologic developments.[21] While this work is still in its very beginning, the possibility of immediate clinical application of the points mentioned is evident. As for its influence upon the current and future studies of the mechanism of the disease, that too is apparent and fraught with infinite possibilities.

The experimental studies on tuberculosis in this laboratory during the past year have all been pursued using the single colony plating method of Petroff, with counted numbers of organisms

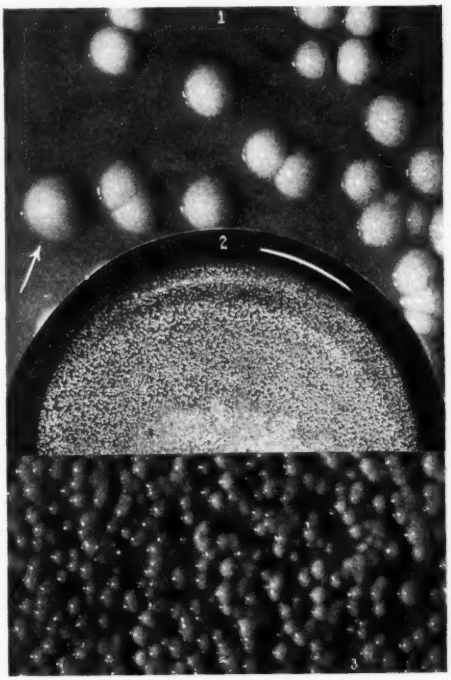

Fig. 55.—1, Avian, strain **A-1, "S" colonies of tubercle bacilli** on Petroff's gentian violet egg media. The colony designated by the arrow is the one from which suspension was made for intravenous inoculation into chickens and rabbits (× 5). 2, Culture from the liver of rooster R 1117, made on the same media as above indicated, thirty-five days after intravenous inoculation of organisms from the colony seen in 1. A pure culture of "S" colonies identical in every respect with the one originally inoculated was recovered (⅔ natural size). 3, Higher power of the "S" colonies seen in 2 (× 5).

from a single picked colony for infecting dosages. Upon inoculating 5,000,000 organisms from an avian A-1 "S" colony (Fig. 55) intravenously into white leghorn roosters, we were

able to recover at autopsy a pure culture of "S" colonies (Fig. 55, 2 and 3) from the lesions found in the liver thirty-five days later (R 1117). Avian A-1 "R" organisms from a single colony (Fig. 56, 4,) were inoculated into rabbits and chickens in the same

Fig. 56.—4, Avian, strain A-1, "R" colonies of tubercle bacilli dissociated from the same original culture, which also produced the colonies of Fig. 55, 1. The arrow designates the colony from which the suspension was made for intravenous inoculation into rabbits and white leghorn roosters (× 5). 5, Culture from the liver of rooster R 1115, thirty-five days after intravenous inoculation with counted suspension of organisms from the colony seen in 4. With the exception of one small "S" colony the entire plate shows characteristic "R" colonies identical in appearance with those of 4 (⅔ natural size). 6, Detail of colonies seen in 5. The arrow indicates the "S" colony (× 5).

dosage as the "S." Thirty-five days later pure cultures of "R" organisms were cultivated from the bone marrow of one rabbit

(R 1125) and from the liver of one chicken (R 1115) with the exception of one "S" colony in each instance. Figures 56, 5 and 57, 7 show the culture plates, Figs. 56, 6 and 57, 8 illustrate more

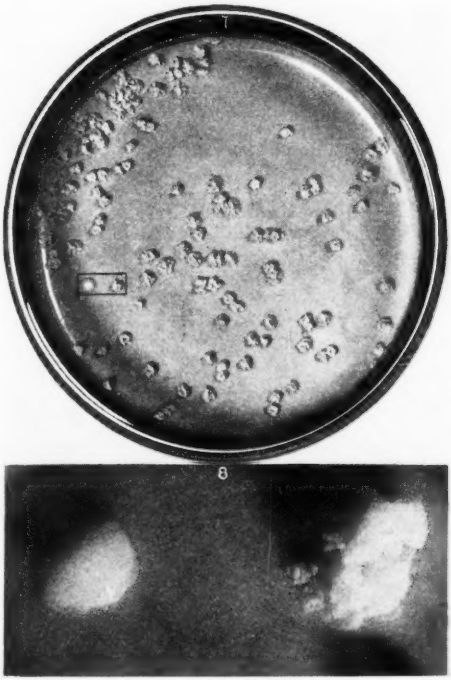

Fig. 57.—7, Culture from the right humerus bone marrow of rabbit R 1125, thirty-five days after intravenous inoculation with organisms from colony (Fig. 56, 4). It will be noted that all the colonies are typically "R" with the exception of one with "S" characteristics. There has been a slight modification in the colony structure since passing through the rabbit. The "R" colonies from the chicken more nearly approximate in structure the original avian "R," but both belong in this category ($\frac{2}{3}$ natural size). 8, Detail of "R" and "S" colonies from 7. This evidence would indicate that a typical avian "S" colony and organisms had differentiated within the body of this rabbit, which had received only organisms from an "R" colony (× 5).

clearly the character of the "S" colony as it contrasts with the "R" colonies. The differences already noted between "R" and

"S" colonies of consistency, emulsification, and staining reaction and morphology of bacilli characterized in every detail these "R" and "S" colonies deriving from animals which had received only infection from a single "R" colony. Studies of the electrophoretic mobility velocities of organisms from each of these two colonies by Dr. Morton C. Kahn, of Cornell University, showed differential values which correlated with his original observations on the "R" and "S" avian dissociates.[22] The animals infected with "R" and "S" organisms were kept isolated in separate rooms throughout the experiment. Such evidence, therefore, seems to support the theory that within the animal body the "R" organisms have shown a beginning tendency to revert to typical "S," though only one out of an actual count of 100 colonies from R 1125 is "S."

Five million counted organisms of a fifteen-day culture from the "S" colony of Fig. 57, 7 and 8 were given intravenously to each of two rabbits (R1250, 1258), and a like number of organisms from the adjacent "R" colony were inoculated into rabbits R1262 and 1270. Thirty-three days later rabbit R1250 died showing typical tuberculous blood changes: an anemia, 6000 monocytes per cu.mm. of blood, and an M/L index of 0.9 (original index 0.130). The organs as found at autopsy are shown in Fig. 57*b*, 11. The spleen weighed 16.2 Gm., the liver was greatly enlarged, and all organs and tissues showed extensive miliary tuberculosis. Cultures from each organ showed a pure culture of typical "S" colonies (see culture from liver, Fig. 57*a*, 9). Rabbit R1270 had shown no blood changes during the same period (original M/L index 0.180; thirty-three days after 5,000,000 "R" organisms M/L index 0.166), but was killed for direct comparison with R1250. The organs as found at autopsy are seen in Fig. 57*b*, 12 to show no gross evidence of tuberculosis. When cultures from organs, such as the liver, were made with amounts of tissue emulsion roughly comparable to those employed in R1250, only one to three colonies appeared on each plate inoculated, and all with the typical morphological characteristics of "R" (Fig. 57*a*, 10). The second rabbit (R1258) injected with suspension of "S" organisms died with miliary tuberculosis eight

days following the death of R1250, or forty-one days after inoculation, with typical blood changes, M/L index 2.30. The culture plates made from the organs of this animal were identical

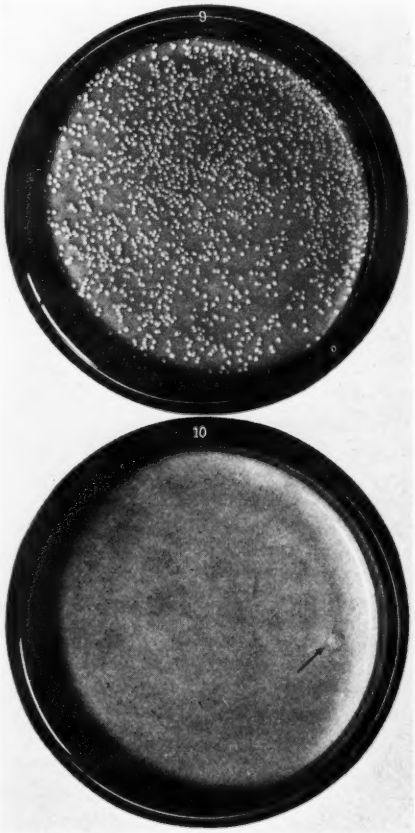

Fig. 57*a*.—9, Culture from the liver of rabbit R1250 thirty-three days after intravenous inoculation with 5,000,000 organisms from fifteen-day culture colony "S" Fig. 57, 7 and 8. All colonies typically "S." 10, Culture from the liver of rabbit R1270 thirty-three days after inoculation from fifteen-day culture colony "R" Fig. 57, 7 and 8. One typical "R" colony, indicated by the arrow, grew out.

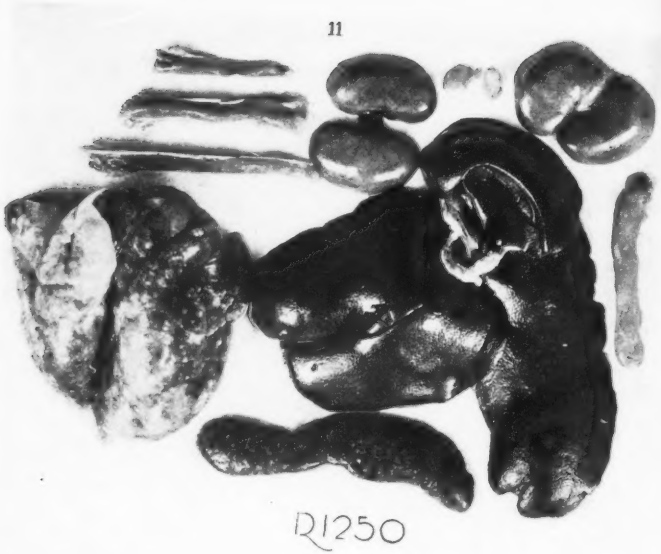

Fig. 57*b*.—11, Gross autopsy findings in rabbit R1250, which died of miliary tuberculosis thirty-three days following infection with organisms from the "S" colony of Fig. 57, 8, obtained from rabbit R1125 originally infected with 5,000,000 organisms from "R" colony Fig. 56, 4. 12, Gross autopsy findings in rabbit R1270, killed thirty-three days following infection with organisms from the "R" colony of Fig. 57, 8. No increased virulence is demonstrated for the "R" colony derived from one animal passage of an original avian "R" dissociate.

with Fig. 57*a*, 9. Rabbit R1262 is still living ninety days after infection without typical blood changes as yet.

The conditions within the body which may favor the change from "R" to "S," or the reverse, present a fertile and important field for future investigation. It is here that the biological work and the M/L index concept meet the newer bacteriological studies. Work now in progress in the laboratories here and at Trudeau is definitely planned to correlate and integrate these observations. As a corollary it is only necessary to mention the dangers inherent in any method of vaccination with living tubercle bacilli, however avirulent they may seem, in the light of these recent bacteriological studies. So long as there remains any possibility of a change in virulence under the influence of environmental or other circumstances, no living virus should be used as a preventive or therapeutic measure.

THE DATA TO BE DERIVED FROM *x*-RAY STUDIES

In addition to careful cellular and serological studies of the blood and tuberculous fluids and the differential analysis of the acid-fast bacterial flora in any given case, serial *x*-ray plates covering a period of years, particularly in children, are yielding new data. The observations of Opie, MacPhedran, and their associates in Philadelphia, in which entire families, with one or more members showing active tuberculosis, have been followed, now cover a period of five years. In children which have at first shown only a small, vague, apparently quiescent focus, the development of activity which spreads from these primary foci has been noted. This would indicate a change in the environment within the body, or in the virulence or number of the organisms, or a reinfection with more virulent bacilli of exogenous origin in a lesion already extant but inactive for a long period. It is at least possible that the interrelation existing between host and parasite at any one time may change, and the recent bacteriological and pathogenic experiments make it appear as a decided probability. Therefore, such studies as are being made in Philadelphia, in the Chadwick Clinic, Boston, and by Lawrason Brown, at Saranac Lake, as well as in other communities in this

country are gradually providing more and more clinical observations which will correlate with the experimental work and the theories of resistance and immunity which must govern the approach to treatment.

Thus it may be seen that the current work on tuberculosis is not only providing new aids to diagnosis and prognosis, but even more fundamental are the contributions which are being made toward the development of new concepts of the mechanism of immunity. The foregoing résumé is presented not so much as the record of certain accomplishments of the recent past, but rather as the promise of future developments of much greater moment to be anticipated. In perhaps no field of medicine at the moment are current concepts undergoing closer scrutiny, the volume of new experimental evidence accumulating more rapidly, or the theories being held more in a state of flux than in tuberculosis. The clinician should be alert and receptive, but highly critical of the instruments which are gradually being evolved for the analysis and treatment of his tuberculous patients.

BIBLIOGRAPHY

1. White, D. C.: A National Research Program in Tuberculosis, Technical Series No. 9, National Tuberculosis Association, 1929.
2. Sabin, F. R.: Johns Hopkins Hosp. Bull., 1923, xxxiv, 277; McClung, Microscopical Technic, Hoeber, 1929, p. 81.
3. Sabin, F. R., Doan, C. A., and Cunningham, R. S.: Contrib. to Embryol., No. 82, Carnegie Institution of Washington, 1925, xiv, 125.
4. Cunningham, R. S., Sabin, F. R., Sugiyama, S., and Kindwall, J. A.: Johns Hopkins Hosp. Bull., 1925, xxxvii, 231.
5. Doan, C. A., and Sabin, F. R.: Jour. Exp. Med., 1927, xlvi, 315.
6. Rogers, P. M.: New England Jour. Med., 1928, cxcviii, 740.
7. Blackfan, K. D., and Diamond, L. K.: Amer. Jour. Dis. Child., 1929, xxxvii, 233.
8. Morriss, W. H., and Tan, S. H.: Amer. Rev. Tuberculosis, 1927, xvi, 729.
9. Cunningham, R. S., and Tompkins, E. H.: Amer. Rev. Tuberculosis, 1928, xvii, 204.
10. Flinn, J. W.: Ann. Int. Med., 1929, ii, 622.
11. Medlar, E. M.: Amer. Rev. Tuberculosis, 1929, xx, 312.
12. Doan, C. A., and Sabin, F. R.: Relation of the Tubercle and the Monocyte-lymphocyte Ratio to Resistance and Susceptibility in Tuberculosis, Jour. Exp. Med., 1930 (in press).
13. Anderson, R. J.: Jour. Biol. Chem., 1927, lxxiv, 537; 1930, lxxxv, 519 and 529.

14. Sabin, F. R., and Doan, C. A.: Jour. Exp. Med., 1927, xlvi, 645.
15. Anderson, R. J.: Jour. Biol. Chem., 1929, lxxxiii, 169; 1929, lxxxv, 77.
16. Sabin, F. R., Doan, C. A., and Forkner, C. E.: II. The Fatty Acids, the Waxes and the Glycerides, Jour. Exp. Med., 1930 (in press).
17. Pinner, M.: Amer. Rev. Tuberculosis, 1928, xviii, 497.
18. Doan, C. A.: Proc. Soc. Exp. Biol. and Med., 1929, xxvi, 672.
19. Petroff, S. A.: Proc. Soc. Exp. Biol. and Med., 1927, xxiv, 632.
20. Cooper, F. B.: Arch. Path. and Lab. Med., 1926, ii, 382.
21. Petroff, S. A.: Personal Communication.
22. Kahn, M. C., and Schwarzkopf, H.: Proc. Soc. Exp. Biol. and Med., 1930, xxvii, 381.

CLINIC OF DR. W. W. HERRICK

PRESBYTERIAN HOSPITAL

MENINGOCOCCIC INFECTION: REPORT OF A CASE WITH DISCUSSION OF TREATMENT

THIS patient is seventeen years old. He is a student with a family history of no present importance. So far as one can discover he has not recently been in association with any cases of acute illness.

Past History.—At the age of four this patient was admitted to the Presbyterian Hospital because he was very drowsy and a meningitis suspected. A lumbar puncture was done. The spinal fluid at this time was found to be clear, not under increased pressure and with a cell count of five. A diagnosis of serous cerebral leptomeningitis was made. After three days the patient was discharged from the hospital apparently well. At the age of three the boy fell from a window striking the head and was unconscious for twenty-four hours. There were no recognized sequels of this accident. Excepting rather frequent attacks of tonsillitis no evidence of increased susceptibility to infection has been noted. There have been frequent headaches and gastro-intestinal upsets of an ill-defined variety.

Present Illness.—The boy was perfectly well until eighteen hours before admission to the hospital. On the morning of November 26, 1929, there was a sudden onset with frontal headache, anorexia, nausea, vomiting and great weakness. No fever was noted during the day but at night the patient felt feverish and sleep was disturbed by bizarre dreams. The frontal headache became very severe and unlike previous headaches. The patient continued to be nauseated but did not vomit during the day. Toward evening spots were noticed on the arms. A physician was called. The temperature was found to be 101 F. The patient was rational and had no pain excepting headache. Simple remedies were prescribed. Later in the evening the patient's mother found him in a stupor from which he could not be roused. He was lying on his back, perfectly still. Later he lay on his side with legs drawn up. He resisted any attempt to change his position. He again vomited. His neck was found to be stiff. The temperature had risen to 103 F. There was no sore throat and no upper respiratory tract infection preceding or at time of the onset of the illness. At 2 A. M. the following morning the patient was sent to the hospital. He was admitted in coma with a temperature of 102.4

F., a pulse of 76, a respiratory rate of 22. The blood pressure was 130/80. The boy appeared acutely ill, was in deep coma, and lay on the side with head thrown back and thighs and knees flexed. If undisturbed he was quiet, but was very averse to any interference. The body surface, especially the extremities, was dotted with maculopapular spots, having dark hemorrhagic centers 1 to 3 mm. in diameter with round pink zones of varying size surrounding them. These did not blanch on pressure. The mucous membranes were free from any eruption. The bones and joints appeared normal. The pupils were small but equal and reacted to light. The tonsils were small but red. The pharynx was injected and showed a small amount of purulent exudate. The lungs and heart were negative. The pulse rate was slow. The abdomen was not distended and was held tense. No anomalies of the cranial nerves were made out. The reflexes of the upper extremities were normal. The right knee jerk was four plus; the left, one plus. The Babinski was positive on the right; negative on the left. The ankle jerks were exaggerated and equal. The abdominal reflexes were not obtained. The neck was definitely rigid. Kernig's sign was positive. The provisional diagnosis was meningococcic bacteremia and meningitis. The cutaneous test for sensitiveness to horse serum was negative.

The blood count on admission was: Hemoglobin 90 per cent; red blood cells, 4,450,000; leukocytes, 24,900; polymorphonuclears, 89 per cent.

Lumbar puncture at 3 A. M. under gas and oxygen anesthesia showed pressure too high to be measured by the manometer. The cells numbered 22,000; the polymorphonuclear cells, 96 per cent; the fluid was grossly cloudy, the globulin content, four plus. Intracellular and extracellular gram-negative diplococci were found. Similar organisms were recovered on culture and were found to agglutinate with polyvalent antimeningococcus serum from both the New York City and the New York State Departments of Health in a dilution of 1 : 1600. The blood culture showed no growth. Cultures from the throat and nose revealed no meningococci. Thirty cc. of antimeningococcus serum were given intraspinally at once. Thirty minutes later 100 cc. of antimeningococcus serum diluted with an equal amount of saline solution were given intravenously without reaction. Two hours later, at 5 A. M., the condition was improved. The temperature had fallen to 100.2 F. Examination of the *fundus oculi* showed the disk margins clearly outlined, the fundus pale, the vessels engorged. At 11 A. M. 40 cc. of turbid fluid were obtained by lumbar puncture and 22 cc. of antimeningococcus serum injected. During this procedure the patient was quiet, cooperative and rational. At 4 P. M. a second dose of 100 cc. of serum diluted with an equal amount of saline solution was given intravenously without reaction. At 11.30 P. M. lumbar puncture was repeated. Twenty-five cc. of fluid were removed and 20 cc. of serum administered. At 11.15 P. M. the following day, November 28th, 25 cc. of spinal fluid were withdrawn and 18 cc. of serum administered. The fluid was less cloudy; the cells numbered 6100; globulin, four plus; polymorphonuclear 90 per cent. On the following day the spinal fluid showed 2180 cells; polymorphonuclears, 92 per cent. Lumbar punctures were performed on the two following days, the spinal fluid on December 1st being only slightly turbid and containing 371 cells, 82 per cent being polymorphonuclears.

The patient's general condition improved promptly from the beginning of the treatment and within twelve hours of the first serum administration the temperature had fallen to normal and never again went above 100 F. The patient emerged from coma and became rational, the headache gradually yielded, the rash and other evidences of a severe infection cleared away. On November 30th, only four days after the beginning of serum therapy, serum sickness appeared in the form of a widespread urticaria. There was also some edema of the lips and of the tongue. This was relieved by adrenalin.

The patient was discharged December 21, 1929, in excellent condition, free from any sequels of the infection.

DISCUSSION

This case is an example of a satisfactory result in meningococcic infection following early diagnosis and prompt and adequate treatment with specific antiserum. This patient's malady was recognized within twenty-four hours of onset. Although the blood culture was negative, the widespread hemorrhagic rash is good evidence of the bacteremia which is demonstrable in a considerable proportion of cases of this kind. Features of diagnostic importance are: sudden onset; severe prostration; deviation from normal mentality which may, as in this case, amount to coma; a great aversion to light, to noise, and to physical interference. More than in any other infection the patient wishes to be left alone and resents any attempt at movement. The face is lacking in play of expression; the features are tense and rigid. Attempts to move or speak are carried out with a rather characteristic frowning protest. The stiff neck, the positive Kernig sign, frequent absence of abdominal reflexes, were all present in this case. The engorgement of the veins of the retina is of some importance. The high leukocyte count and the hemorrhagic rash are characteristic, as is the sudden onset and the rapid development of grave symptoms. Characteristic, also, is the prompt subsidence of symptoms with serum administration by the intravenous and intraspinal routes.

In this case we were particularly fortunate in dealing with a strain of the meningococcus which was agglutinated in high dilutions by the serum available. Experience has shown that a serum to be effective should agglutinate the organism concerned in a dilution of at least one in fifty. As the meningococci from

this patient were agglutinated by the serum available in the high dilution of one in 1600 we had at our command a very potent weapon, the effectiveness of which is amply shown in the brilliant clinical result. The importance of having at command a serum containing an ample amount of agglutins for the type of organism infecting the patient is one that cannot be overemphasized. In each case one should isolate the organism from the blood stream, spinal fluid, or nasopharynx and make sure of the agglutinin content of the serum to be used for the organism concerned. If this cannot be done, one can depend in a measure upon the therapeutic effect. If the serum does not give a prompt and favorable response, it almost surely does not contain the antibodies desired and should be at once discarded and replaced by a serum from another source, in the hope that another serum will be better adapted to combat the strain of meningococcus which the patient harbors.

The question of the route or routes by which serum should be administered is no longer a matter of debate. Those whose experience has been almost entirely on the laboratory side or who have not been in a position to see examples of this infection in their earlier stages, have been reluctant to adopt intravenous antimeningococcus therapy. On the other hand, those who have had wide clinical experience, especially in conditions where the early phases of the infection are observable, are unanimous in their belief based on experience that large amounts of serum given intravenously in the early stages of meningococcic infections are striking and dramatic in their effectiveness.

The therapeutic program in an average case of this infection might be outlined briefly as follows:

The diagnosis should be established as early as possible. Sensitiveness to serum should be determined by the intracutaneous inoculation of 1/10 of 1 cc. Lumbar puncture should be done immediately, and enough fluid withdrawn to bring the pressure to approximately normal, and an amount of serum 5 or 10 cc. less than the amount of spinal fluid withdrawn, allowed to run into the spinal canal by gravity. If the skin test shows no sensitiveness 100 cc. of antimeningococcus serum diluted with an

equal amount of saline solution should be given intravenously. The first 15 cc. should be administered slowly at the rate of 1 cc. a minute, the physician being alert to any evidence of anaphylaxis. Adrenalin should be at hand. In actual experience serious reactions are infrequent and one runs no more risk in the serum treatment of meningococcemia than in similar treatment of pneumococcic infections. In severe cases, the intravenous treatment should be given every twelve hours for two to four doses depending upon the effect. Each intravenous treatment should be followed by lumbar puncture and the administration of from 20 to 30 cc. of serum. After the first forty-eight hours lumbar puncture should be performed once a day and 20 to 30 cc. of serum administered each time.

If the patient does not make striking improvement in the first twelve hours, the serum should be changed. The average patient will require one or two large intravenous injections and four intraspinal injections. It is usually well to cease intraspinal serum administration when the cells have diminished below 1000, when the organisms have disappeared, and when the percentage of polymorphonuclear cells in the fluid approaches 80. Lumbar puncture may be performed daily or on alternate days for observation lest the infection recur also to reduce intracranial pressure. If evidence of infection persists and does not yield to serum from any source, the prognosis is naturally bad. The same is true if there is evidence of obstruction to the flow of fluid in the subarachnoid spaces. In this event drainage may at times be had by puncture of the cisterna magna. Serum may also be safely given by this route, either alone or in conjunction with the lumbar route. In desperate cases one of the more serious procedures, such as ventricular puncture, may be tried.

Not infrequently one meets examples in which intraspinal therapy is overdone. In this event each intraspinal serum administration is followed by an increase in the signs of meningeal irritation; by more headache, greater rigidity of the neck, back, and extremities, and even by increased mental disturbance. With this is also observed a hypersecretion of cerebrospinal fluid. This is found in great amount, under high pressure and,

usually, with comparatively few cells and without organisms. If cells are present in quantity usually at least 20 per cent of them are of the mononuclear variety.

In this state it is well to cease from all serum administration. Lumbar puncture, if it gives a happy effect in bettering meningeal irritation, may be carried out daily or on alternate days. After one to three punctures, however, it is usually well to omit all interference and let nature alone.

The key to success in the management of this disease is early diagnosis, the use of a serum rich in antibodies for the organism concerned, and the use of this serum in abundant amount both intravenously and intraspinally. Of the success of such treatment this patient is an excellent example.

CLINIC OF DR. WILLIAM R. WILLIAMS

SECOND MEDICAL DIVISION, NEW YORK HOSPITAL

SOME MYOCARDIAL CASES

THE realm of the myocardium is a land of mystery. Here transpire most surprising events. A person who considers himself healthy becomes alarmingly ill and within a minute may die. Another, a chronic myocardial invalid, may stagger along for many years in a state of valetudinarianism. The revelations of the postmortem room have often enough been quite as surprising. Among the lesions found in the hearts of patients of this group the condition of the coronary arteries is of first importance. These arteries may be narrowed and rendered less elastic by arteriosclerosis, they may be almost or quite closed by thrombi formed at the site of damage or by emboli carried from some point in the vascular channels more or less remote. These changes may appear in a coronary artery of any size or in any part of the heart and be followed by changes in the heart muscle. Thus we find degeneration and atrophy of the muscle fibers, infiltration with leukocytes, or replacement by connective tissue scars. Such lesions are frequently found at autopsy. They may be large or small, single or many. Some seem quite recent, others of slow development and long standing. All of these lesions presumably are due to cutting off the supply of blood from a part of the myocardium. The changes in the larger coronaries and the scars are seen easily in the ordinary postmortem examination. There is, however, great difficulty in examining the tiny vessels immediately related to the degenerated areas. Such a study would entail the careful inspection under the microscope of countless serial sections. The pathologic department even of the best hospitals is scarcely able to find time for this great work.

On the clinical side also the picture varies. Cases of sudden death are met with in patients who have given no observable symptoms of cardiac disorder. Others have a sudden attack of striking symptoms from which they may or may not rally. Some may even seem to be restored to health for a long time.

The development of electrocardiography has quickened our interest in this group of patients and has been of great help in defining the nature of the lesion and in locating its site within the heart. Often it is also quite helpful in prognosis. We hope for further development along this line.

It may be worth while to review a few case histories that fall into this category and compare with them the records of the autopsies. Such cases are not uncommon but only a few selected from the files of the second medical division at New York Hospital will be mentioned in this article.

Case I.—A woman of fifty-nine years was admitted to the wards one afternoon at four o'clock and died eleven hours later. She was a patient in a diabetic clinic and was taken ill during one of her regular visits. She suddenly was seized with sharp precordial pain and oppression, the pain radiated to the left shoulder and down the left arm, her breathing became very difficult, she grew dizzy and fainted. She was at once carried to the ward, and regained consciousness promptly. The physical signs indicated edema of the lungs, the râles from which were so noisy that no heart sounds could be heard. The pulse was scarcely felt, it was very small and irregular and could not be counted accurately. Attempts to determine the blood pressure were unsuccessful. The blood count showed red cells, 6,450,000; hemoglobin, 90 per cent; leukocytes, 23,700; polynuclears, 50 per cent; lymphocytes, 45 per cent; large mononuclears, 5 per cent. The urine, obtained by catheter, showed specific gravity 1.024; acid; albumin, trace; sugar, none; a rare hyaline cast; numerous leukocytes and a rare red blood cell. The temperature was 99.8 F. by rectum, the respiration rate about 26. Within two or three hours the lungs cleared somewhat, but still no heart sounds could be heard, and the prostration persisted. The pain remitted for a while but in the evening the pain and dyspnea again became more severe and she died at 3 o'clock.

The electrocardiogram taken a few minutes after she was admitted to the ward is reproduced in Fig. 58. It shows a complete auriculoventricular block with an auricular rate of about 100 and a ventricular rate of 27. There were occasional premature ventricular beats. The Q. R. S. portion of the curve was abnormally widened and was notched. The T wave shows no isoelectric level after S. This suggests occlusion of a branch of a coronary artery.

Autopsy Protocol.—Anatomic diagnosis: Coronary sclerosis, myocardial fibrosis, arteriosclerosis, fatty degeneration of the liver, congestion of the

lungs, chronic cholecystitis, cholelithiasis, occlusion of cystic duct and mucocele. Each pleural cavity contains about 50 cc. of clear serum. The pericardium contains 100 cc. of straw-colored serum. The heart is twice the size of the patient's fist and cardiac fat is extensive. The muscle of the wall is less than 1 cm. thick. Section of the muscle of the heart shows areas of diffuse fibrosis throughout the walls of both chambers but more in the left ventricle. There is much fibrosis below the aortic valve in the region of the conducting fibers. On the whole the color of the heart muscle is good. The mitral valve shows shortening of the cusps and shortening and thickening of the chordae tendineae. The sclerosis of the cusps is at the base and appears as smooth plaques. The aortic valve has similar plaques on the peripheral side of the aortic ring. Around the mouths of the coronary arteries are small

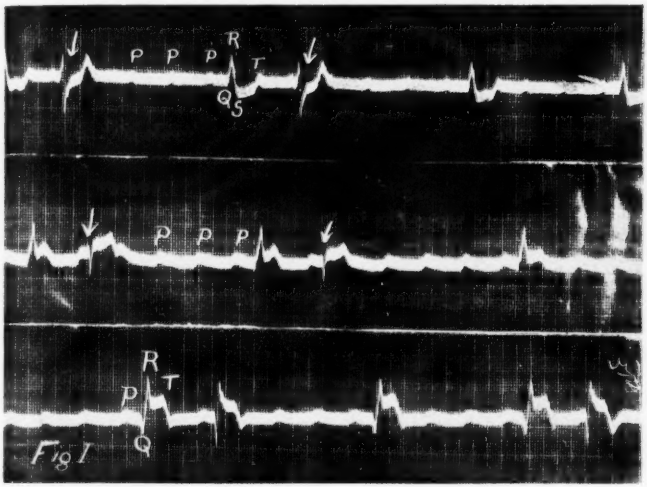

Fig. 58.—Case I. Complete auriculoventricular block. Premature ventricular beats (at the arrow) Q.R.S. wide and slurred. S.T. not at basic level.

yellowish plaques of sclerosis. On dissecting out the coronaries extensive sclerosis and calcification are found in all branches but particularly in the descending branch of the left coronary. Histologic examination: The muscle cells are pale, pigment is small in amount. Some areas are fragmented. There is slight intercellular fibrosis in spots.

The lungs are congested. The liver weighs 2300 Gm., the lobules cannot be distinguished. Microscopically there is marked fatty infiltration and degeneration. The gallbladder is of normal size and contains a stone which occludes the bladder drainage. The gallbladder contains thick mucoid liquid with only a trace of bile pigment, its wall is thickened and adheres closely to the stone. The pancreas shows no gross changes excepting that

it is small. The kidneys show the lesions of the arteriosclerotic contracting kidney.

Comment.—This patient was a diabetic under treatment in the diabetic clinic and her urine was sugar free. She had old heart and arterial lesions but was well enough to undertake the journeys to the dispensary. While there she became suddenly very ill and although she rallied somewhat she died within eleven hours. She had a remarkable electrocardiogram. The heart showed lesions that must have been present for a considerable time. She had a gallstone and diseased gallbladder that seemed to have caused no noticeable symptoms.

Case II.—This patient was admitted to the hospital on four separate occasions, the first on November 3, 1928. He was a male fifty-nine years old. For seven years he had attacks of spasmodic dyspnea. At first the attacks came at intervals of about a month, later more frequently and worse in winter. For the past few months he had an attack every night upon going to bed. Until the past fortnight subcutaneous injections of epinephrine relieved but for the past two weeks his physician gave him morphine.

His blood pressure has been known to have been high for seven years. For the past six months there has been edema of the legs for the first time and some constricting precordial pain. He denied an earlier history of asthma hay fever, rheumatism or heart symptoms, although he admits being susceptible to attacks of bronchitis for many years.

The reason for coming to the hospital was the spasmodic dyspnea rather than the pain over his heart. On admission there was much wheezing over the lungs and signs of liquid in the left pleura. The heart was enlarged, the left border being 12 cm. to the left of the midline. At the apex there was a harsh systolic murmur heard well into the axilla. The aortic second sound was louder than the pulmonary. The rate was from 76 to 90, and the blood pressure 180/120. There were extrasystoles. The reflexes were normal and moderate edema of the legs was present. The liver was moderately enlarged. The urine contained albumin, casts, a few leukocytes. The phenolsulphonephthalein test showed 20 per cent excretion in two hours. The blood count showed 14,300 leukocytes with 80 per cent of polynuclears, the hemoglobin was 86 per cent, the Wassermann was negative, blood urea nitrogen 12 mg. per 100 cc. The temperature was slightly elevated with a maximum reading of 100.5 F. by rectum. Left thoracentesis removed 1150 cc. of clear serum. The electrocardiogram (Fig. 59) showed normal sinus rhythm with occasional ventricular extrasystoles, normal conduction time, slurred Q. R. S.; left axis deviation and abnormal inversion of T in leads I and II. The shape of the ventricular part of the curve is such as is interpreted to mean bundle branch block presumably of the right branch of the auriculoventricular bundle.

He was out of bed on the fifth day and left the hospital on the eighteenth day without edema and feeling quite comfortable. While at his home his

symptoms returned and he had a little more pain which was greater on the right side than on the left. He returned to the ward on December 27th and 1000 cc. of liquid was removed from the left pleura. He again improved, was out of bed on the eighth day and went home on the twelfth day feeling quite comfortable. Again all the symptoms recurred and on February 1, 1929 he returned to the hospital. On the next day 650 cc. of serum was removed from the left pleura. He was tapped again on February 9th but practically nothing was found.

Upon this admission the urine showed no albumin, sugar or casts, in fact it was quite normal. His blood pressure was 190/100, the leukocytes 10,000 with 68 per cent of polynuclears, the hemoglobin 70 per cent, and the electrocardiogram about the same. He, however, showed some mental con-

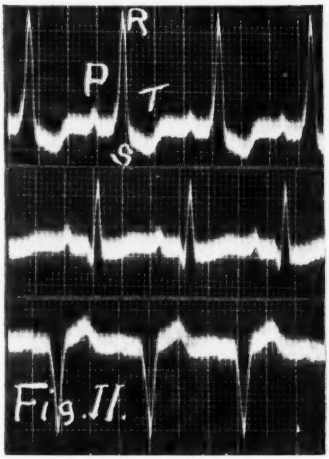

Fig. 59.—Case II. Normal sinus rhythm. Q.R.S. slurred. Left axis deviation. Abnormal T.

fusion with difficult speech and some aphasia. These symptoms were ascribed to sclerosis of the cerebral arteries and disappeared before he left the hospital. At the time of his discharge on February 14th it was obvious that his recuperation was less satisfactory than during his previous sojourn in the ward.

This time he stayed home for seven weeks with a steady increase of all of his symptoms. Upon his final admission on April 4th the dyspnea was marked, there was liquid in both pleurae and the peritoneum, and there was an extensive edema of the lower part of the body. His left chest was tapped and 500 cc. of serum was removed. The general edema cleared very promptly and within a week disappeared. He felt surprisingly well. On the night of April 17th he suddenly became very weak and died within a few minutes.

Autopsy.—Probable cause of death: Coronary sclerosis. Many lesions were found throughout the body. There was a little clear liquid in the right pleura, 300 cc. in the left and about 100 cc. in the pericardium. The lungs were emphysematous, of a yellowish brown color and contained pigmented cells. Each kidney contained two small infarcts in the cortex and the lesions of the arteriosclerotic kidney. The aorta was atheromatous and showed much calcification throughout its entire length. The heart was very large, weighing about 700 Gm., the wall of the ventricle being greatly thickened. Three infarcts were found each about 4 cm. in diameter, a very recent one on the lateral edge of the left ventricle, and two old ones in the septum. The mitral valve was quite sclerosed and seemed incompetent. The aortic valve was fairly normal, but just above it was marked atheroma with a small ulcerated area. The coronaries were markedly sclerosed and calcified and several branches showed almost no lumen but no thrombus was found.

Comment.—This patient was ill for many years first with spasmodic dyspnea relieved by epinephrine, with bronchitis, emphysema, hypertension, and mitral regurgitation, but no severe pain. About five months before death symptoms of cardiac decompensation were more in evidence, periods of remission recurring until death. At the end sudden death supervened after one of the periods of promising improvement.

On gross dissection of the heart the autopsy showed three distinct infarcts of considerable size. Histologically one at least was very old and another one not very recent. There were no sudden or startling symptoms to mark the times at which these occurred. The symptoms suggested rather a gradual impairment of the circulation. It is probable that the third infarct may have precipitated the death of the patient.

Case III.—Male fifty-one years old, a diabetic. In September, 1928 toward the end of a heavy meal the patient was overcome by a sense of pressure around the chest and broke into a profuse sweat. He recovered after a short rest, but has not been wholly well since. There have been attacks of dyspnea especially after a hard day's work. He had had no orthopnea, edema, cough or hemoptysis. His previous history contained nothing of moment.

On the day of admission to the hospital, March 25, 1929, he was awakened from a sound sleep with a choking retrosternal distress, a sense of constricting band around the chest, shortness of breath, apprehension of death, a severe aching pain over the heart that radiated to the shoulders and down the inner side of both arms to the wrists. He could not keep still but kept walking up and down the room in spite of the difficulty of breathing. He summoned a physician who gave him relief by morphine hypodermically. The patient

was so impressed by the attack that he insisted upon coming to the hospital. Upon admission his face was somewhat dusky, there were coarse râles over the lungs at the bases with dulness, diminished fremitus and breath and voice sounds. Reflexes were normal. The cardiac apex beat could not be seen, but was vaguely felt. The heart dulness extended 12 cm. to the left of the midline. The sounds were faint, the pulse rapid, 120 per minute, small but seemingly regular, the blood pressure 120/80. No edema was found in the extremities. The temperature was 102 F. by rectum. The blood count showed 15,000 leukocytes with 80 per cent polynuclears. The blood Wassermann was negative; blood sugar 300 mg. per 100 cc. The urine had a specific gravity of 1.040, contained no albumin, but there was 1.2 per cent of sugar.

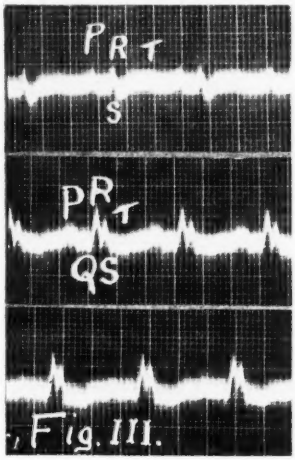

Fig. 60.—Case III. Normal sinus rhythm. Q.R.S. wide, notched, slurred. T wave inverted in leads II and III.

The electrocardiogram (Fig. 60) showed simple tachycardia with a rate of about 100, normal auriculoventricular conduction time, Q. R. S. wide, notched and slurred, the T wave was inverted in leads II and III and had the shape that suggests coronary occlusion.

For a while his condition improved very much and sugar disappeared from the urine but he complained of almost constant pain in the heart. He found it hard to eat because eating seemed to aggravate this pain. On April 12th he began to complain of the return of shortness of breath. While eating breakfast on April 22d he had an attack of pain and dyspnea and died after five minutes.

Autopsy—Probable cause of death, coronary sclerosis. Other lesions: Generalized arteriosclerosis, infarcts of heart and lungs, sclerosis of pancreas. Small thrombi adherent to the walls of the vessels are present in the lowest

branches of the left pulmonary artery. There is a somewhat larger thrombus, which also is organized, caught over the first branching of the right pulmonary artery. The origin of this is not clear. Its size and shape correspond approximately to the pulmonary artery just above the point where the thrombus was caught. The thrombus is about 6 cm. long but only loosely adherent.

Heart: Weighs 500 Gm. and appears superficially to be of about normal color. There is about 40 cc. of fluid in the pericardium. On section fairly large adherent thrombi are found in the right auricular appendage and also one in the left ventricle, considered to be of antemortem origin. The wall of the left ventricle shows several markedly changed areas. On its lateral border there is what appears to be a fairly old infarct. On its anterior border the appearance suggests a much more diffuse process as it is mottled red and yellowish. Most of the septum between the right and left ventricles is a white soft mass in which no red areas are present. The coronary vessels show very marked atheroma and calcification. The main branch of the left coronary is especially small, but there is very small lumen still present. No coronary thrombosis is found grossly. No peripheral origin for a thrombus such as that found in the right pulmonary artery is found. Pancreas shows sclerosis of island of Langerhans.

Comment.—This patient shows several small infarcts of the left lung which are adherent and therefore not very recent and a larger one of the right lung. The heart shows at least three infarcts whose appearance suggests widely different times of formation. One would expect every one of these to have caused symptoms of sudden onset. Clinically only three attacks could be traced. The one in September, seven months before death, may have been due to the fairly old infarct on the lateral border of the left ventricle. If so he worked rather hard for several months after this although he did have a good deal of precordial discomfort. The attack on March 25th was doubtless due to one of the other infarcts. These two attacks are quite typical of coronary occlusions. The rather definite return of shortness of breath on April 12th and the sudden death may be attributed to the third infarction of the heart or to the pulmonary infarctions, but it is difficult to definitely apportion the symptoms to the separate lesions.

Case IV.—This patient was a man of seventy years. Ten years ago he had rheumatism in several joints and for several years he had a dry cough. About a year ago he began to notice a "full feeling in the upper part of his stomach with a feeling of pressure upward" that would come on after a heavy meal and was accompanied by gas and indigestion. This feeling came more

frequently, he noticed some dyspnea on exertion, palpitation, and edema of the feet, but no cardiac pain at any time. His chief reason for coming to the hospital was the full feeling in the stomach. Examination showed about what one would expect to find in an old man whose organs were showing the effect of time—wheezing breathing, enlargement of the heart, a soft systolic mitral murmur, accentuated aortic second sound, beaded arteries and somewhat elevated blood pressure (164/110), edema to the knees, a large liver probably from congestion, a normal temperature, a slight secondary anemia and a negative Wassermann. The electrocardiogram (Fig. 61) showed marked left predominance and an inverted T wave in lead I which suggested damage to the myocardium.

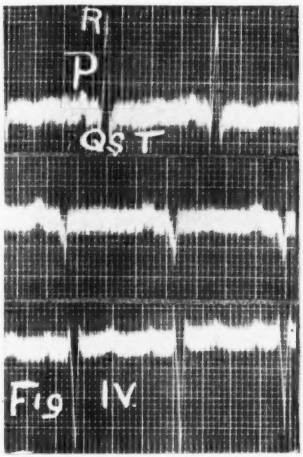

Fig. 61.—Case IV. Normal sinus rhythm. Left axis deviation. T wave inverted in lead I.

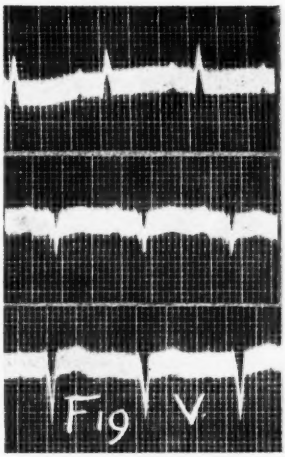

Fig. 62.—Case IV. Six months after Fig. 61. Striking loss of voltage.

After twelve days in the ward the edema had disappeared and he felt quite comfortable and planned a trip south. For four months he got along very well except for slight dyspnea on exertion and lack of strength. The symptoms of decompensation increased steadily, the edema extended upward to the waist, his left arm became swollen, dyspnea increased, he could not lie down and he returned to the hospital in very poor condition. The blood pressure was now 200/100, the phenolsulphonephthalein test showed an excretion of only 10 per cent in two hours, although the blood urea N was only 16 mg. per 100 cc. The electrocardiogram was similar to the first one excepting for a marked reduction in the amplitude of the curves. He failed to improve and died waterlogged four days after admission.

Autopsy.—Probable cause of death—fibrous replacement of heart muscle,

coronary arteriosclerosis. The other lesions were such as might have been expected from the clinical observation—general arteriosclerosis and chronic passive congestion of the liver, kidneys, and other organs. The heart itself was very interesting. It was large weighing about 700 Gm. Its shape was peculiar in that the left ventricle toward the apex was unusually large and rounded. On cutting through this about one third of the ventricle toward the apex showed extensive fibrous replacement evidently representing a large area once softened. It was grayish white in color and showed small cystic areas. The coronaries showed marked sclerosis with thickened calcareous plaques and small lumina.

Comment.—This patient showed such symptoms as one would expect to find in an old man with evidence of arteriosclerosis and accompanying changes in the heart with decompensation. There was no abrupt attack of any sort, nevertheless the heart showed a very extensive localized lesion in the wall of the left ventricle, which should have been due to occlusion of the coronaries supplying this portion of the heart. Probably this change in the coronaries was of slow development and the heart adapted itself to it gradually but incompletely, as was shown by the slow appearance of symptoms of decompensation.

DISCUSSION

This small group of cases shows fairly well the variations in the symptoms to be expected in coronary disease. The abrupt occlusion of an artery should cause more or less shock as an important part of the attack. The symptoms referred to the heart are pain and other forms of distress. Such pain may be epigastric, retrosternal or felt in any part of the cardiac region, it may radiate to the shoulders and arms on one or both sides. The distress varies. Case I described it as "oppression," Case IV as a full feeling in the epigastrium "with pressure upward," Case III as a constricting band around the chest. The heart action is disturbed, often rapid, sometimes slow, often irregular and almost always weak. Breathing is difficult, the lungs are congested or edematous. "Indigestion" is a very common complaint, perhaps in the milder attacks the most common one. Shock is quite sure to be present and the patient seems weaker and more ill than the original attack would lead one to expect. The heart efficiency is impaired for considerable time. This is

well illustrated in Case III. The electrocardiogram is of great help here. Immediately after the attack it may look normal, but after a day or two characteristic changes will appear. This delay in the appearance of electrocardiographic effect is not uncommon, and therefore an electrocardiogram taken very soon after a heart attack cannot be relied upon to exclude a diagnosis of coronary occlusion.

If the narrowing of the artery is gradual it would seem that there may be no abrupt attack at any time and the symptoms are those of a slowly failing heart.

Just how to treat cases of coronary occlusion with success is not clear. The gradual cases are treated as any decompensating heart. In an acute attack an effort must be made to relieve the patient's distress. Morphine seems to be the best drug for this. At times the nitrites seem to help. After the attack rest until the readjustment of the circulation may take place is indicated. It is however impossible to know how long this inactivity should be insisted upon. Case III resumed work after a day or two and continued to work for six months before having another attack. Recently we have had two patients who were kept in bed several weeks after attacks of moderate severity. One of these insisted that he felt perfectly well after two or three days and was quite resentful because of the enforced inactivity. A few days after leaving the hospital and resting at home he went to a moving picture show and died suddenly there. The other was very neurotic. After the acute attack he complained of mild pain over the heart that persisted for weeks. A few days after his discharge he also died suddenly. To offset these cases we have records of others who have done well after a protracted rest in the hospital.

Our faulty prognosis depends upon our ignorance of the exact lesion in the heart. We do not know whether there are detachable clots on the walls of the heart, on the valves or on the rough spots of the coronaries themselves; we do not know the extent to which the lumen of the coronaries is narrowed by sclerosis. Then, too, there is the possibility of spasm in diseased and narrow coronaries of which our knowledge is incomplete.

CLINIC OF DRS. I. W. HELD AND A. ALLEN GOLDBLOOM

BETH ISRAEL HOSPITAL

PATHOGENESIS OF PEPTIC ULCER

PEPTIC ulcer is an extremely frequent disease. It is an affection encountered by every practitioner in the routine of daily work. Yet its pathogenesis is still almost wholly problematic. Diagnosis with the most modern means encounters difficulty and, in a fair proportion of cases, failure. Quite a large percentage of the ulcers treated medically recur, and after surgical treatment there is also a fair percentage of recurrence, proving that neither treatment is wholly satisfactory. So, year after year, important medical and surgical congresses discuss various phases of the problem and, month after month, the literature on the subject becomes more and more voluminous. Our defense in adding to the latter—which at the beginning gives us the feeling of attempting to contribute sand to a Sahara—is that we hope, in some measure at least, to assist in clarifying prevailing conceptions of the pathogenesis of this puzzling malady.

From the pathologic point of view the term "peptic ulcer" includes not only gastric but duodenal ulcer, peptic ulcer of the lower end of the esophagus and postoperative marginal (gastrojejunal) and jejunal ulcer. Regarding pathogenesis, it does not matter whether the ulcer is gastric or duodenal, but from the standpoint of complications and surgical procedure the exact localization of the seat of the ulcer is of the utmost importance.

Medical science, through a knowledge of pathogenesis, has been able to do much toward eradicating diseases of a specific bacteriological nature. Unfortunately, however, a specific bac-

teriological cause cannot be claimed for peptic ulcer. So a number of theories regarding its etiology have arisen. Most of these are based upon a great deal of experimentation with regard to which clinicians have aligned themselves into an almost eternal triangle. Some reject all deductions from animal experimentation on the unsubstantiated ground that disturbed function of the lower animal does not resemble that of the human being. Others are inclined to be influenced by almost any statement based on laboratory experiment, be it test tube or animal. Still others, with a background of experimental study and clinical experience, neither overthrow nor accept dogmatically; instead, they discriminate and adapt the results of worthy experiments to clinical practice and apply them properly.

If we belong to the group of clinicians who weigh the results of the careful experiments—and most of us do—there are a number of theories regarding the pathogenesis of peptic ulcer that cannot well be disregarded. These fall readily into two groups, theories which although not proved experimentally have become so vital a part of our clinical thinking that we cannot conceive of the etiology of peptic ulcer without reverting to them, and a miscellaneous group not so important and yet not wholly negligible because they assist us to an understanding of the causative factors in a certain number of cases. To the latter group, for example, belong the anemic, occupational and direct trauma theories; to the former, the vascular, neurogenic spasmogenic, bacteriological, toxic, chemical, catarrhal, mechanical, internal secretory and constitutional theories.

VASCULAR THEORY

The vascular theory originated with Virchow and Cohnheim. These authors, based on extensive postmortem experience, advanced the theory that peptic ulcer is due to an embolus or a thrombus interfering with local circulation and thus leading to infarction of the gastric area supplied by the vessel by exposing it to digestion by acid secretions. Originating in the minds of such authorities, this theory was long without contradication. Indeed, today some of the Virchow pupils—notably Hauser and

Ceelen—are still of the opinion that in almost every case of peptic ulcer the chief causative factor is a diseased localized blood vessel producing nutritional disturbance.

Ceelen contends, specifically, that in most cases the arteriosclerotic vessel in the vicinity of the ulcer is the primary cause. It is true that ulcer occasionally originates on the basis of an arteriosclerotic vessel but most of the autopsy material on which Ceelen rests this convinction has been obtained from individuals who died of an intercurrent disease at an age when general arteriosclerosis is common. Hence the vascular changes in the stomach were more than likely merely part of a general arteriosclerosis. It is likewise probable that the arteriosclerotic changes in a blood vessel in the vicinity of a peptic ulcer may be secondary to the ulcer and consequently pathologic changes of the blood vessel in the neighborhood of an ulcer may be encountered in individuals who have no general arteriosclerosis. In other words, the direct, demonstrable pathologic changes in the blood vessels in the immediate vicinity of an ulcer may be the effect of the ulcer and not its cause. The effect that an ulcer may produce in neighboring blood vessels may be, and often is, so severe as to erode all its walls and lead to hemorrhage. It is also well known to pathologists that arteriosclerotic changes in the gastric vessels are the exception, even in cases of general arteriosclerosis. It is also important to remember that other diseases where the changes in the vascular system are rather common—such as, for instance, lues, polyvascular disease like thrombo-angiitis obliterans—gastric ulcer is not a very common accompaniment, with the exception of the so-called "purely syphilitic ulcer." Syphilitic gastritis plays little, if any, rôle as an etiologic factor in peptic ulcer. The reason why this is not the cause of ulcer is probably the anacidity and even achylia that is generally present in these cases. In those cases of tabes dorsalis where gastric hemorrhage is occasionally encountered postmortem examination fails to show the presence of peptic ulcer.

From the foregoing statements, however, it should not be implied that the vascular theory can be abandoned because without disturbance in the local nutrition, the occurrence of

ulcer cannot be conceived. The existence of definite pathologic changes in the blood vessels, such as arteriosclerosis or the presence of an embolus, need not be present. In the vast majority of cases functional vascular disturbances are present in the stomach even though postmortem examination fails to show the presence of peptic ulcer in some of the cases. A purely functional disturbance of localized blood vessels may spastically so close the vessel as to interfere with local circulation. These functional vascular changes are favored by a number of factors, very important among them being the anatomical position of the vessels.

ANATOMICAL POSITION OF THE VESSELS IN THE STOMACH

Hauser and his pupil, Busch, studied the relation of vascular emboli to infarction. They made the highly interesting observation that an embolus generally occurs in a region where a very

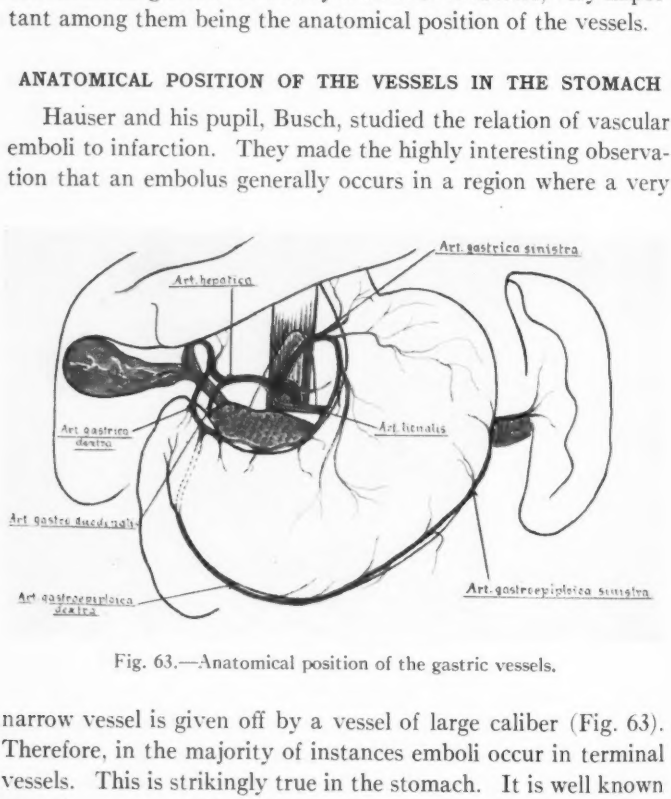

Fig. 63.—Anatomical position of the gastric vessels.

narrow vessel is given off by a vessel of large caliber (Fig. 63). Therefore, in the majority of instances emboli occur in terminal vessels. This is strikingly true in the stomach. It is well known that the area in which ulcer usually occurs has the poorest blood supply of the entire stomach and that the vessels in that region

are terminal. If a vessel nourishing only the mucosa or submucosa is affected by an embolus or thrombus, superficial ulceration results which may heal rapidly and, while present, give rise only to such transient symptoms as to escape attention. This would explain the finding of healed ulcers in the form of small scars on the lesser curvature of the stomach or duodenum in approximately 30 per cent of autopsies. If a vessel nourishing the deeper gastric or duodenal structures is involved, the resulting ulcer is more extensive and may lead to necrosis, perforation or extensive scar tissue formation.

Katsch objects to this anatomical conception on the ground that although the fornix of the stomach has areas in which the gastric vessels are terminal, this region is seldom the seat of ulcer. It seems to us that Katsch's objection is invalidated by the fact that the activity of the stomach is not equal in all parts. Consequently, abuse of the stomach is not identical in all regions and the effect of diminished vascularization is, therefore, not alike in every part of the organ. It is also true that the blood stream, due to the position of the stomach, may be more rapid in the fornix, an important factor in counteracting embolus. In the pars media (saccus digestorius), pylorus, and duodenum the formation of an embolus is favored because the blood stream is much slower in the smaller vessels on account of their anatomical location. This anatomical location of the vessels is alone insufficient, however, to explain why embolus or thrombus should lodge in these vessels in only certain individuals and not in others. The embolus is certainly not carried there from some distant gland or infected thrombus, as is the case in multiple erosions of the stomach in severe infections and sometimes after operations. There is also no reason to assume that a local disease of the blood vessel wall or some localized chemical change exists in the blood which would cause the formation of a thrombus in the blood vessels. There is left only one probable explanation of the impediment in the circulation of these localized blood vessels and that is spasm of the blood vessel.

NEUROGENIC THEORY

It was to explain this spasm that the neurogenic theory was advocated. Experimental as well as clinical and postmortem observations have attributed an important causative rôle to organic changes in the vagus supplying the stomach. Von Yzeran indirectly cut the vagus below the diaphragm and produced gastric erosions. Erosions and hyperemia have also been produced by injuring the base of the brain, thereby indirectly influencing gastric secretion. To this group of experiments belongs the injury caused to the vagus by pharmacological methods, namely by injection of pilocarpine into rabbits or over-stimulation of the sympathicus by adrenalin, causing erosions in the stomach or duodenum. As is often the case, an equal number of careful observers, carrying out identical experiments, failed to get the results of the original experimenters. For instance, E. Klein, although having cut the vagus below the diaphragm of a dog, was unable to produce any lesion in the stomach or duodenum.

Direct pathologic changes in the subdiaphragmatic portion of the vagus have been found by some in cases of peptic ulcer. Singer goes so far as to state that in most cases he found enlarged tuberculous glands pressing on the gastric vagus. He attributes the formation of the ulcer to the pressure of these glands on the vagus. The fact remains, however, that the experimental basis of section of the vagus below the diaphragm to bring about peptic ulcer is uncertain, and that proof of direct pathologic changes in the vagus either as a result of disease of the vagus proper or due to pressure from without is very scant. The findings of Singer of enlarged tuberculous glands in the vicinity of the ulcer are accepted, but it must be remembered that in the postmortem material in Vienna, where tuberculosis is so prevalent, tuberculous glands are found in other parts of the body as well. It seems to us that there is no reason to connect the finding of glands in the vicinity of the stomach, even close to the subdiaphragmatic vagus, as proof of their interference with the function of the vagus. The innervation disturbance of the local blood vessels would seem to us to be one of a purely functional nature without any demonstrable organic changes in the vagus.

This conception has been especially fortified within the last twenty years by the epoch-making work of Eppinger and Hess on the relation of the vegetative nervous system to clinical medicine. This substantiating work of Eppinger and Hess led von Bergmann to promulgate the following highly important spasmogenic theory.

SPASMOGENIC THEORY

According to the von Bergmann spasmogenic theory, it is not essential for the nerves supplying the blood vessel to be demonstrably diseased or injured by pressure from without. The nerves, however, may be so functionally disturbed as to cause marked spastic contraction of the vessel of sufficiently long duration to bring about ischemia of the area supplied by the vessel and eventual autodigestion and ulcer formation. If the vessel is of small calibre, the affection is only transient and the resulting ulcer heals rapidly, leaving no scar. If large vessels are involved, the affection is more protracted and a deep-seated ulcer may result.

The spasmogenic theory has received almost universal recognition, particularly since pharmacological proof of an imbalance in the vegetative nervous system in the ulcer individual has been furnished by Katsch, Kalk, Westphal, and other pupils of von Bergmann, as well as by Glasser, J. Kauffman, Winkelstein and many others.

Durante studied seventeen possible ways of producing ulcer experimentally and arrived at the conclusion that ulcer may be produced by any agent capable of damaging the sympathetic nervous system as it is on the integrity of this system which controls circulation, secretion, and profound sensibility in the stomach that the very life of the gastric cell may be said to depend.

It was stated above that the stimulus of the spasmogenic theory of von Bergmann was furnished by the work of Eppinger and Hess. The extensive experiments on animals and the testing of the action of specific drugs (pilocarpine, atropine, and adrenalin) on the autonomic nervous system of the human carried

out by Eppinger and Hess furnished clinical evidence of the important rôle of the autonomic nervous system in the mechanism of symptoms of an individual organ. Eppinger and Hess showed that an imbalance in the autonomic nervous system may be responsible for symptoms originating in any organ without the presence of pathologic changes in the organ. They divided individuals into two groups: Vagotonic and sympathicotonic. Before long, however, it became apparent that a pure vagotonic or a pure sympathicotonic individual does not exist. The same individual may show instability of the vagus in one organ and of the sympathicus in another or—and this is more important—he may have in one organ at one time symptoms of instability of the vagus and at another time sympathicus instability. The terms "vagotonic" and "sympathicotonic," therefore, had to be modified. Von Bergmann suggested describing individuals with an imbalance in the autonomic nervous system as individuals with *vegetativ stigmatisiert*, that is, with stigmata in the autonomic nervous system.

Whatever modification the original work of Eppinger and Hess had to undergo, it nevertheless stimulated research into clinical and biochemical problems. In the latter field, Kraus and Zondek showed the relation of the electrolytes to the autonomic nervous system which implies that in order to permit the physiologic antagonistic action between the vagus and the sympathicus necessary to bring about a balance in the action of the organs, the proportion of electrolytes (calcium to potassium and magnesium to sodium) must be maintained. They brought out the fact, also, that organs of internal secretion play a most important rôle in maintaining the electrolytic equilibrium, and, also the equilibrium of the autonomic nervous system. The interrelation of these three systems is so close that in determining the function of the organs the three must be thought of as one. Hence Kraus proposed the term *vegetative system* to include all three. In some individuals there may be a primary affection of the autonomic nerves, in others, of the glands of internal secretion, and in still others of the electrolytes. This disturbance may often depend upon some underlying disease, for example,

individuals with metabolic disturbances may have a primary imbalance in the electrolytes. The so-called "neuropath" may have his instability in the autonomic nerves, while some, again, may have an actual disease of one of the organs of internal secretion. The individuals who have definite disturbance in the organs of internal secretion—thus also disturbing the autonomic nerves and the electrolytes—can easily be recognized clinically, and the relation of such disturbance to organic disease elsewhere is easily explained. Hyperadrenalanemia, on account of suprarenal hyperfunction which may cause duodenal ulcer with its accompanying mononucleosis, as studied experimentally and clinically by G. A. Friedman, although rather rare, belongs to this group. This is true, too, of thyroid hyperfunction when associated with gastric ulcer and polynucleosis. It is much more difficult, of course, to demonstrate clinically dysfunction or imbalance in the autonomic nerves alone as a cause of organic disease. There is, however, no doubt that such imbalance can cause a functional disturbance of the blood vessels which, if prolonged, will lead to organic change.

Clinical proof of this has been brought forth by surgeons (H. E. Isaacs, personal communication) who, while operating on the stomach, have encountered—particularly in the region of the ulcer-bearing area—pale, almost white ischemic areas due to local spasm. The area of ischemia has been seen to persist for several minutes, followed suddenly by a return of circulation, although at times no return of circulation was noted. Still no ulcer would be detected by the surgeon. These are the individuals who so frequently return within a few months of a futile exploratory operation, not only with outspoken symptoms, but with definitely demonstrable *x*-ray signs of an ulcer. We have had such cases return within a few weeks of operation. Because of the local ischemia they have almost unbearable pylorospasm or gastrospasm far out of proportion to the pain of the ordinary ulcer, simulating the extreme pain of tabes dorsalis or of gallstones. These patients do not bleed and no roentgenological sign of ulcer may be seen for some time.

Even pathologists, who see only end-results and not function,

were fascinated by the spasmogenic theory. The first to acknowledge it was Roessle who claimed that peptic ulcer is a secondary disease (ulcus ventriculi, *eine zweite Krankheit*) due to spasm in the muscularis mucosa which in turn compresses the neighboring blood vessel. Such spasm in most cases, according to Roessle, is not of necessity caused by any intrinsic disease in the stomach proper, but is brought about reflexly by either a chronically diseased appendix or gallbladder, or, in a large number of cases, by both. The frequent association of chronic gallbladder disease and chronic appendicitis with peptic ulcer has long been known to clinicians. Recently, Hartman and Rivers of that clinic brought out important statistical proof of the frequency with which this triad exists.

Von Bergmann and Roessle differ only as to whether the spasm is primarily in the blood vessels or in the muscularis mucosa. From the clinical standpoint the differentiation may seem *a priori* to be more of academic than of practical value. Nevertheless, it is not unimportant. If we accept von Bergmann's conclusion that the spasm is primarily in the blood vessels, it would explain the local ischemia encountered by the surgeon and also many of the severe symptoms that occur in a state of ischemia without the presence of a definite ulcer. It likewise explains the depth and other pathologic changes of the ulcer.

Of course, we do not deny that muscle spasm can exist without primary neurogenic vascular disturbance. That it can was proved experimentally by Kurt Meyer when he paralyzed the vagus of animals by atropine injections. To be certain of the paralyzing effect of the atropine, Meyer injected the animals with pilocarpine and, seeing no vagus response, next injected foreign proteins. He succeeded in bringing about muscle spasm, demonstrating that allergy anaphylaxis can cause spasm of the muscle. Regarding the injection of foreign proteins into the blood vessels, the allergic phenomena manifest themselves by dilatation of the small vessels (arterioles and capillaries), whereas ulcer is an ischemic manifestation due to spasm of the vessel. These are, therefore, two entirely different phenomena. Kurt Meyer's work is valuable chiefly from the standpoint of vascula-

changes caused by foreign proteins in the process of allergy as indicated by angioneurotic edema, urticaria, or the gastrointestinal symptoms encountered in Henoch's purpura or the intestinal symptoms associated with erythema multiforme (Osler).

CHEMICAL (HYPERACIDITY) THEORIES

In view of the fact that peptic ulcer is frequently accompanied by hyperacidity and that even where no demonstrable hyperacidity exists symptoms of hyperacidity are often present, it was natural to associate both conditions and to regard hyperacidity as a precursor and even as a cause of peptic ulcer. Indeed, some experimenters and clinicians consider hyperacidity the main cause of ulcer; others not only deny its importance as a causative factor, but go so far as to claim that it is not of necessity an accompaniment of gastric ulcer and deny the importance of hyperacidity in causative relation to peptic ulcer. Clinically, such a view is unjustifiable.

Careful workers in the study of gastric secretions, stimulated by the work of Rehfuss and his co-workers, and by the histamine method carried out by many authors and recently in a most conclusive way by Cheney, have shown beyond doubt that in the majority of cases there is an actual hypersecretion curve in gastric ulcer, especially in duodenal ulcer. The continuous secretion curve originally demonstrated by Rehfuss, although not present in a large number of cases of duodenal ulcer, can be brought out by the injection of histamine. This would demonstrate that even when hypersecretion is not present the slightest exogenous stimulant, such as histamine, or even any mental excitement or seasonal changes, may suffice to bring on the hypersecretory curve. This would tend to show that clinically there is a definite relation between the acid gastric secretion and peptic ulcer.

The fact that in some individuals with ulcer there is normal acidity and in others sub- or an-acidity does not indicate that hyperacidity was not present before the ulcer started, or during its early period. It may only signify that some additional factor was present bringing about diminished acidity. This may be,

for example, associated gastric catarrh with an excess of mucus or, in rare cases, occult oozing of blood into the stomach which may be detected only chemically. It is possible that in the individuals in whom acidity is less than normal, or in whom there is anacidity, the ulcer has been present for so long a time that there is exhaustion of acid secretion.

It seems to us that hypersecretion and its necessary accompaniment, hyperacidity, are the result of an imbalance in the autonomic nervous system. The underlying vagotonia may produce these conditions without the presence of an ulcer, but where there is an underlying tendency or diathesis to ulcer, such hypersecretion and hyperacidity greatly favor its occurrence. Imbalance in the autonomic nervous system may explain why an existing hyperacidity alters to sub- or an-acidity. The imbalance in the autonomic system varies in the same individual. At certain times, the vagus influence predominates; at other times, the sympathicus. During the early, active life of the individual the imbalance is usually on the vagus side. Later in life (during the phlegmatic period) the sympathicus predominates. Studies on gastric secretions of healthy individuals have demonstrated that in late middle life and in old age gastric acidity is considerably lowered. It is reasonable, therefore, to assume that individuals afflicted with peptic ulcer in whom, during early life, the vagus influence predominated, with a resulting hypersecretion and hyperacidity, may later in life be subject to imbalance in the sympathicus with hyposecretion and subacidity because the acid quantity is almost directly proportionate to gastric secretion. Even so close a clinical observer as Deaver has emphasized the great importance played by hyperacidity in the causation and symptomatology of ulcer. Deaver believes that the dysfunction of the pyloric sphincter interferes with regurgitation of the intestinal alkali secretion to neutralize the gastric contents, and that if hyperperistalsis does not succeed in emptying the stomach and ridding it of excessive acid secretion, ulcer may result. In this connection, the work of Palmer of Chicago is interesting. He introduced dilute hydrochloric acid through the duodenal tube into the stomach of individuals

afflicted with ulcer and produced immediate symptoms characteristic of the lesion. This procedure is certainly not advisable for diagnostic purposes, but it revealed the violence with which the stomach reacted to an increase of acid. It could not have been the introduction of the additional quantity of hydrochloric acid, however, that brought on the symptoms. These must have been produced by the stimulating effect of the added hydrochloric acid so that there was an increase of gastric secretion.

Experimental proof has long existed as to the relation of hyperacidity to peptic ulcer. Mann and Williamson have recently made a further very important contribution to our clinical understanding of the relation of gastric secretions, particularly acidity, to peptic ulcer. They were able to produce ulcer in dogs by severing the pylorus and connecting it with the duodenum or by connecting the stomach with the jejunum. Wherever the acid contents were allowed to flow freely into the duodenum or jejunum an ulcer resulted, even when the greater part of the stomach was cut away so that only a small part of the fornix (pars cardiacum), containing acid-secreting glands, remained. If the entire stomach was removed and the esophagus was connected with the jejunum or duodenum no ulcer resulted. Thus was acid demonstrated as an ulcer-producing factor. Mann and Williamson found, also, that the ulcer had a tendency to heal when the acid was discontinued and that this healing tendency was disturbed if the secretions were allowed again to reach the ulcer. It may be mentioned here that in 1914 one of the authors (Held) while working with J. Romer in Professor Bickel's laboratory in Berlin, experimented also with the object of allowing the gastric acid contents to flow freely into the duodenum. For this purpose the pyloric sphincter of three dogs was destroyed in order to keep the pylorus permanently opened. In one dog, killed two weeks later, marked erosion of the first portion of the duodenum was found. This experiment was not reported because war broke out at that time, and the lesion was not sufficiently studied pathologically to justify publication. It is mentioned here merely to point out the significance of the work of Mann and Williamson and that the

relation of hypersecretion to peptic ulcer from the diagnostic and therapeutic standpoints must not be regarded with indifference. Indeed, it should be considered as highly important.

The work of Mann and Williamson, originating in this country and being of such vital importance in relation to the pathogenesis of peptic ulcer, has been followed up with great interest by Aschoff and his pupils, particularly by Buchner. Aschoff and his pupils injected histamine into fasting rats and caused an increase in gastric secretion and hyperacidity. They were able to produce peptic ulcers of ranging depths. Aschoff differentiated five zones of the mucomembranous system of man which he termed "the gastral system," stating that of these only the corpus glandular zone is a source of secretion of hydrochloric acid and pepsin. This part cannot be digested by gastric secretions, but in the other four parts erosions can result from hyperacidity in the hunger state.

Buchner has demonstrated that if hypersecretion or hyperacidity are brought forth by stimulating the glandular secretory region situated in the corpus the pyloric region is the one where erosions result. These erosions resemble pathologically the lesions found in the pyloric region described by Konjetzny and Puhl as catarrhal lesions resulting in ulcer but not caused by acid. Buchner and his co-workers agree with Konjetzny and Puhl as to the existence of these erosions but make the definite statement that they are caused by the acid secretions, based on their exact pathologic studies. Further proof that an excess of acid secretion in the corporic region may bring about erosions in the pyloric region of a similar nature has also been demonstrated by R. Kaufmann in the clinic of von Bergmann. He caused extensive skin burns in animals, setting free cholin or histamine which, he states, stimulated gastric acidity and so produced an ulcer. Interesting, also, is the work of Kalk, who showed that irritation of the skin in the human may produce marked hyperacidity. The relation of hyperacidity to the production of erosions and even ulcer is exemplified in those rare cases in which Meckel's diverticulum is lined with gastric mucosa. When this is the case it is a real reproduction in nature of Pavlov's small stomach

pouch. In his small stomach, as is well known, Pavlov demonstrated that although the small stomach is separated from the large stomach, secretions result in the small stomach, or pouch, if the large stomach is stimulated. In a Meckel diverticulum lined with gastric mucosa, acid secretion results when the gastric secretion is stimulated. This acid secretion, however, in Meckel's diverticulum erodes, eventually digests the mucous membrane, and leads to deep ulceration and perforation. We see, therefore, that living tissue can be digested by acid secretions and that thrombi in the vessels with resulting infarction of surrounding areas need not be present.

Applying the excessive acid secretion to the pathogenesis of ulcer in the human at first causing erosions and later ulcer, the question arises: Why do not these erosions occur in all parts of the stomach? The answer to this is likewise given by Aschoff and his pupils, namely, that in the lesser curvature, anterior and posterior wall, where the mucous membrane appears in large folds an anatomical protection against erosion exists. Furthermore, the mucus secretion is here more pronounced, tending to neutralize the acid. In the areas where erosion and eventual ulcer formation do occur, the mucous membrane is not characterized by folds and has, therefore, less mucus secretion, so that it is predisposed to erosion.

Still another question, however, arises. Why does the erosion and eventual ulcer formation occur in some and not in others? Buchner's answer is that so long as the secretion in the corpus of the stomach, and in the pyloric glands and in Brunner's glands in the duodenum, is normal no ill effect of the acid can result. When, however, abnormal psychical influences disturb the gastric secretions or there is abuse by food or by some other factor, erosions and eventual ulcer formation can result.

We have dwelled at this length on the relation of hyperacidity to the pathogenesis of peptic ulcer not because we accept this as the only outstanding cause but because the tendency on the part of some has been to ignore entirely the relation of hyperacidity to pathogenesis, despite the fact that the work of Mann and Williamson has conclusively demonstrated the prominent

rôle played by the acid factor and its importance in the therapeutic management of peptic ulcer.

During the last few years the work of Balint, leading directly to therapeutics, is of increasing interest and importance. According to Balint, the tissues of the individual afflicted with ulcer are more acid than those of the normal individual. As it is impossible during life directly to test the acidity of tissues, Balint instituted an indirect method of testing it. He administered intravenously to the fasting patient 20 cc. of an 8 per cent sodium bicarbonate solution and determined the p_H and titration acidity in the urine two hours before infusion and two hours afterward. The urine of a normal individual after such an injection is alkaline whereas that of an individual afflicted with ulcer remains acid. Balint has concluded that the reason the alkali does not appear in the urine is because the tissues of the ulcer-individual retain it. Many authors, particularly Westra, have tested the Balint phenomenon and have found it correct. However, Westra does not entirely agree with Balint's interpretation of the cause of the phenomenon. He believes that the bicarbonate effusion unloads and drives out calcium from the tissues, thereby driving out the acid element. In this way, it influences the autonomic nervous system in the sense of vagus stimulation. In other words, the Balint phenomenon is not only a sign of a disturbance in the acid base equilibrium but is an indication of imbalance in the autonomic nervous system.

DIGESTIVE FERMENTS

Regarding the activity of digestive ferments in relation to the etiology of peptic ulcer, the very interesting work of Katzenstein stands out prominently. He advanced the theory that it is possible for pepsin to digest the gastric mucosa and cause gastric ulcer in some individuals and not in others because of a marked diminution or even absence of antipepsin in such individuals. Based on his experimental findings, he produced a chemical antipepsin which he employed for therapeutic purposes. The results obtained by others who have tried the product have not been such as to favor its continuance. In reality, Lorber

has demonstrated that it is not the antipepsin which prevents the pepsin from digesting the mucous membrane, but bicarbonate of soda. The work of Lorber is interesting, of course, because of the support it lends the rational use of bicarbonate of soda in hyperacidity conditions and in gastric ulcer.

Stuber believes that gastric ulcer is the result of regurgitation of the pancreatic ferment—trypsin—into the stomach at a time when acidity is at its lowest point. He bases this conception on extensive personal experiments and on the work of Boldyreff who proved that there is always regurgitation of intestinal contents and pancreatic ferments into the stomach which are, however, made inactive by the acid in the stomach. When, during certain stages of digestion, acidity is at its lowest point, trypsin—being a very active ferment—may cause digestion of the mucous membrane and lead to ulcer. Whereas, theoretically and perhaps experimentally, under wholly favorable conditions, trypsin digests mucous membrane that is not ordinarily in contact with the ferment, there is no clinical reason to accept this theory. In the first place, peptic ulcer is practically always accompanied by gastric acidity and even by hyperacidity in what Deaver terms "the preulcerative stage." The findings of Von Eiselsberg also offset the trypsin theory. Von Eiselsberg, as is well known, in conjunction with gastro-enterostomy for gastric ulcers, closed the pylorus with the object of preventing the acid contents from passing the pylorus and entering the duodenum. He was trying in this way to obviate the irritation of the ulcer-bearing area by the gastric acid chyme. However, by doing this he also prevented the regurgitation of duodenal alkaline secretion into the stomach. The result was a gastrojejunal ulcer, or even recurrence of pyloric ulcer, or the formation of a new ulcer on the lesser curvature unless nature was benevolent enough to reopen the pyloric sphincter. We see, then, that regurgitation of intestinal contents is rather beneficial, just as the secretion of a normal quantity of mucus which reduces acidity. In most cases of gastro-enterostomy the aim is to reduce the acidity because of the regurgitation of intestinal contents through the jejunum into the stomach. The trypsin theory of ulcer formation may apply

to the rare ulcers encountered in the second or third portion of the duodenum, particularly the ulcer at the duodenal-jejunal junction, but it cannot be accepted as an etiologic factor of peptic ulcer.

TOXIC THEORY

The injection of foreign proteins and other toxic substances into animals, thus causing gastric erosions, led to the conception that similar toxins develop in the human as a result of absorbed end-products of digestion and may cause peptic ulcer. This theory would have gained little ground without the work of Bolton of London, who experimentally produced a substance from the triturate of gastric mucosa which he called "gastrotoxin," and which, when injected into the blood of animals, produced lesions of the stomach. As far as animals go, the Bolton experiments are enlightening and interesting, but the application of this theory to human peptic ulcer is of questionable clinical value.

Some have advanced the theory that toxins arising from organs other than the stomach, particularly from the liver, may be the cause of peptic ulcer. Gunderman—stimulated by the experiments of Friedrich and Engelhart—ligated the main left branch of the portal vein of rabbits, and caused atrophy of the liver. In one of the animals acute ulcer of the stomach resulted. The animal survived forty-eight days. The ulcer had the same pathologic characteristics as peptic ulcer in man and so Gunderman concluded that normally toxic substances are formed in the liver which, when its function is normal, are nonpoisonous, but which may produce gastric ulcer when the liver is diseased.

The liver toxic theory deserves emphasis because of its clinical significance. It has been assumed that an increase of bilirubin in the blood always speaks against ulcer, and is very important in the differential diagnosis between biliary affections and peptic ulcer. Many authors, however, have found that in complicated cases of peptic ulcer during the state of active symptoms, there may be a marked increase of bilirubin in the blood. This would clinically support Gunderman's conception that in certain cases at least there is a transient dysfunction in the

liver in case of ulcer. This may also explain the actual frequent association of biliary duct disease and gastric ulcer, and why in some cases of duodenal ulcer the Graham dye is not taken up by the gallbladder even when injected intravenously. Such dysfunction in the liver or biliary ducts need not be due to organic disease, but may be the result of—as believed by many, particularly by Westphal, a temporary functional disturbance of the sphincter of Oddi which interferes with the flow of bile, and even to motor functional disturbance of the gallbladder (dyskinetic gallbladder disease). Duodenal ulcer as well as gastric erosions, secondary to severe skin burns, would also find their explanation in a loss of the disintoxicating function of the liver.

The acid theory as revived by Aschoff and his pupils and the toxic theory especially pertaining to the diminution of the disintoxicating power of the liver may explain the occurrence of erosions in the stomach and duodenum, but they do not account for chronic peptic ulcer. According to Aschoff all chronic ulcers are preceded by superficial erosions. Clinically, it is difficult to accept such a version although it comes from an authoritative source. The erosions caused experimentally, whatever the method, or such as occur clinically in severe infections or after operations are scattered chiefly on the anterior and posterior wall, more rarely throughout the greater curvature, and are very superficial. They are practically never encountered on the lesser curvature of the stomach, which is the favored site of chronic peptic ulcer.

The toxic effect of chemicals, such as carbon monoxide in the production of acute ulcers, must be mentioned although it bears no relation to chronic peptic ulcer.

BACTERIOLOGICAL THEORY

It was natural in an era of bacteriology to seek the cause of peptic ulcer in specific micro-organisms. Experimenters brought forth proof that the invasion of different micro-organisms can in reality cause erosions in the gastric mucosa, but it was soon found that these micro-organisms produced similar erosions in the rest of the gastro-intestinal tract and that the erosions were

merely the expression of the toxic effect of an excessive number of bacteria in the blood. The bacteriological work of preeminence in relation to peptic ulcer is that of Rosenow and his co-workers. Rosenow applied his theory of the selective affinity of streptococci producing lesions in different organs to peptic ulcer and actually produced peptic ulcer by injecting rabbits intravenously with streptococci obtained from gastric ulcers in humans. However, it is our belief that even streptococci with selective affinity for the stomach are not the true cause of ulcer, and that Rosenow's work is of greatest value from the standpoint of prophylaxis. If an ulcer exists, streptococci can prevent its healing or be the cause of more extensive ulceration.

Askanazy advanced the theory that inasmuch as fungus mucoidis is often discovered in the ulcér it should be considered a cause. It is more reasonable to assume that in cases of chronic peptic ulcer, particularly those associated with marked gastric retention, the fungi—if present—are secondary and not primary factors.

CATARRHAL THEORY

Konjetzny and Puhl, on the basis of extensive pathologic studies, advanced the theory that gastric catarrh is present in practically all cases of peptic ulcer and that gastritis is a forerunner of ulcer. Furthermore that this gastritis is usually located in the prepyloric and pyloric region and is present in all cases of ulcer. In some it cannot be demonstrated macroscopically, but it is microscopically visible in every case. This theory came as a surprise to both clinicians and pathologists. At present many pathologists, among them Hauser, and many clinicians, among them von Bergmann, do not concur. We do not feel justified in taking a controversial stand regarding pathologic findings. Yet it is impossible to explain the symptom complex and the sudden relief of symptoms in gastric ulcer if gastric catarrh is a forerunner and a constant accompaniment of every ulcer. Based on the Konjetzny theory, surgeons have advocated subtotal gastrectomy, irrespective of the location and extent of the ulcer. There is no question that in chronic gastric ulcer the immediate vicinity of the ulcer may show catarrhal changes. In a number

of cases as shown by Aschoff and his pupils even the pyloric portion may be the seat of microscopical catarrh. It may possibly be that such catarrhal changes may be responsible for the spreading of the ulcer, but that the original ulcer should start on the basis of catarrh seems most unlikely. According to Konjetzny himself the catarrh is present throughout the entire stomach in many cases of gastric ulcer. Why then should just one small part of the stomach be the seat of an ulcer? The presence of catarrh in gastric ulcer has been confirmed by Aschoff and Buchner and their co-workers. However, they regard the ulcer the result of hyperacid gastric secretions on the basis of catarrh leading to ulcer.

MECHANICAL THEORY

In view of the fact that peptic ulcers are situated in those parts of the stomach that have what Aschoff calls physiologic narrowings and are subjected to pressure by the surrounding organs, Aschoff advances the theory that if an erosion of the mucous membrane—whatever the cause—begins in the locality of these physiologic narrowings, healing is mechanically interfered with and a chronic ulcer results (Fig. 64). These narrow-

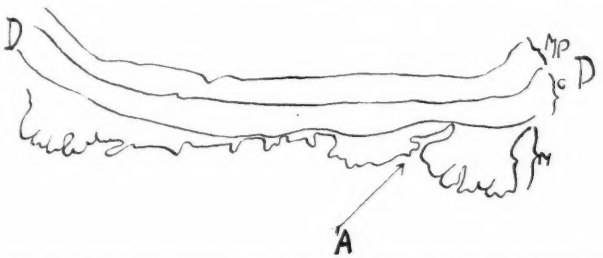

Fig. 64.—Ulcus ventriculi after Aschoff: *P*, Proximal part of the ulcer; *D*, distal part of the ulcer; *M*, mucosa; *C*, connective tissue; *Mp*, muscularis propria; *A*, undermined brim of the proximal part and direction of progress of the ulcer by passage of the chyme wave.

ings are caused at the antrum cardiaca by diaphragmatic pressure, at the lesser curvature by pressure of the abdominal aorta; at the pylorus by the spine, and at the duodenum by the head of the pancreas. The flow of chyme, forcing itself mechanically

through these narrow regions, may cause the early erosion (hyperacid kind). As the chyme continues to bathe the ulcerated area, it may by sheer force cause irritation of the proximal rim of the erosion and bring about proliferation, thickening, and grinding off of the distal part until it appears lower than the proximal part (Fig. 64). Thus it acquires the so-called "funnel" shape.

This theory of Aschoff is not absolute because in many cases the ulcer occurs in parts of the stomach not directly subjected to pressure influences. Moreover, it occurs in individuals in whom the stomach is ptosed so that even the areas of narrowing are not in a vicinity where pressure influences from neighboring organs play a rôle. Pathologically, the funnel-shaped ulcer with its base directed distally is, as demonstrated by Hauser, the exception and not the rule. Consequently the passage of chyme in a certain direction cannot be a sole cause of the progression of the ulcer and of further pathologic changes determining its shape. However, to deny the theory of Aschoff in its entirety is unjustifiable. It does explain chronicity in certain individuals in whom there is persistent pressure from neighboring organs, as in the hypersthenic individual or the extremely asthenic individual, which prevents the ulcer from healing.

OCCUPATIONAL THEORY

The mechanical theory of Aschoff may well be linked with the old, established occupational theory for it has long been known that occupation that compels a sitting posture and continuous pressure against the epigastrium, as for instance the occupation of the shoemaker or chauffer, may predispose the individual so occupied to ulcer. That position actually does cause pressure on the pars media was demonstrated by Hitzenberger and Reich when roentgenographically they found that the sitting posture causes an artificial hour-glass contraction, and that the greatest pressure is exercised on the lesser curvature, thus explaining the frequency of ulcer in this region. It must be remembered, however, that the external pressure is but one factor in the predisposition of an individual to ulcer; otherwise ulcer

would be a much more frequent occupational malady than it is.

In this connection, one must be particularly careful not to be swayed by false impressions. One may happen to see several patients with gastric ulcer who follow an identical occupation and from this conclude that chauffeurs, let us say, are as a whole more liable to this disease than another group of people. Another, who does not have chauffeurs as patients, may entirely doubt this conclusion. However, statistics from large clinics and from postmortem material have repeatedly emphasized the fact that sitting occupations where pressure is exerted against the epigastrium may occasionally be responsible for gastric ulcer.

It must be remembered, too, that it is not wholly the occupation causing pressure from without that ulcer may occur in individuals following certain callings. The mode of life may be such as to force the individual to bring about injury to gastric secretions and motility by virtue of improper food eaten at improper hours and in an unwise manner. Quick eating or eating under excitement will in the majority of cases greatly mechanically disturb the motor and secretory functions of the stomach and indirectly force the system to assimilate food in an unassimilable form, thereby producing toxic effects which, in turn, bring about permanent lesions in the stomach that lead to peptic ulcer. This would explain the frequency with which ulcers occur in traveling salesmen, cooks, etc. That eating when one is in a marked state of excitement causes hyperemia and capillary dilatation in the stomach has been demonstrated experimentally by Ottfried Muller and his pupils. When they produced marked vasoneurosis in animals pronounced hyperemia in the stomach and ulcer resulted. The secretory changes produced in the stomach by improper food and an improper mode of eating are especially detrimental to the first portion of the duodenum, and to the jejunum in case of gastro-enterostomy. If one's habit of eating is such as to pour hyperacid gastric contents into the first portion of the duodenum persistently, he may look forward to a resulting irritation of the duodenum and possible eventual duodenal ulcer (Hurst).

DEPRIVATION OF VITAMINS

With further reference to the influence of certain forms of diet on the formation of ulcer, experimental work has demonstrated that a prolonged deprivation of vitamins—particularly vitamin C—producing scurvy can also produce ulceration in various parts of the gastro-intestinal tract. Such conditions have been encountered in man. In reality, however, although the vitamins are of indisputable importance in the process of food assimilation the extent to which a human being can endure the deprivation of certain vitamins without any objective pathology tissue changes, although subjective symptoms may occur, is remarkable. The direct relation of vitamin C deprivation to ulcer in the human is not greatly important, clinically, although individuals with certain inherent constitutional factors will show the ill effects of deprivation much sooner than others.

DIRECT TRAUMA TO THE STOMACH

To the mechanical factors causing gastric ulcer may be added direct trauma to the stomach. This may sometimes be the starting point of ulcer.

EPIGASTRIC HERNIA

That epigastric hernia may clinically, and even roentgenographically, simulate gastric ulcer led A. V. Moschowitz to a careful study of the clinical aspects and anatomical causes of the symptoms of epigastric hernia. He arrived at the conclusion that in the majority of cases this lesion alone is responsible for gastric ulcer symptoms, a conclusion which was at first widely accepted. Added experience has shown that where ulcer symptoms are very severe in association with epigastric hernia, both lesions are present. Whether there is a causative relation between the two cannot be stated with certainty. In view of the fact that, as shown by A. V. Moschowitz, epigastric hernia causes traction on the falciform ligament of the liver, it may be assumed that toxic disturbances in the liver are produced which, in turn, cause gastric irritation. If this irritation is continued sufficiently long it may lead to actual ulcer formation. From the practical stand-

point, this is highly important. If a patient has persistent gastric symptoms in the presence of an epigastric hernia, the hernia should be corrected surgically. In that way at least one etiologic factor in the formation of peptic ulcer is excluded.

ANEMIA

Anemia has long been considered an etiologic factor in peptic ulcer. This conception is traceable to the erroneous diagnosis of chlorosis in the presence of gastric symptoms, whereas in reality the existing anemia was probably due to occult bleeding from an ulcer. The real ulcer, however, was diagnosed only when a hemorrhage took place. As this was an infrequent occurrence the anemia instead of being really a consequence of ulcer was interpreted as a cause of ulcer. However, there is no plausible reason to associate any form of anemia with the causation of ulcer.

GLANDS OF INTERNAL SECRETION

The glands of internal secretion have been exhaustively studied from the standpoint of their causative relation to peptic ulcer. Noteworthy in this regard is the work of G. A. Friedman who found that destruction of the suprarenals leads to duodenal ulcer and that removal of part of the thyroid leads to gastric ulcer. Fright has been found to cause erosions in the gastric mucosa of rabbits, attributed to stimulation of the sympathicus which causes a sudden increase of adrenalin in the blood, thereby interfering with the emptying of the affected organ. Such persistent emotional disturbances may even lead to actual pathologic changes. In this way one can explain primary functional disturbance in the suprarenals which leads to disturbance in the sympathicus and so interferes with the motility of the gastrointestinal tube. Clinically, however, one does not encounter the association of thyroid dysfunction with gastric ulcer often enough to establish an etiologic realtionship. Neither does one encounter disease of the suprarenals in the form of hyperfunction in association with duodenal ulcer.

CONSTITUTIONAL THEORY

We have so far dwelled on the important experimental data in relation to clinical facts in connection with the pathogenesis of peptic ulcer. As the discussion has progressed, we have become increasingly impressed by the fact that each theory—be it vascular from Virchow to von Bergmann and Roessle, the acidity theory as revived by Mann and Aschoff, or the catarrhal theory of Konjetzny—has an important place in the general scheme if one is to understand the pathogenesis and therapeutics of peptic ulcer. These theories are not merely of historical or academic significance. Yet, if we were to remain with these theories alone, no matter upon what extensive and authoritative experimental data or clinical observations they might be based, we should still be confronted with many problems in the pathogenesis of this disease. For the solution of these, some other factor must be sought.

Certain diseases to which the human is heir cannot be reproduced in the animal because the primary underlying factors reside in mankind. So far as mankind is concerned, some nationalities and races are more afflicted with certain diseases than are others. In Russia and Norway ulcer is much less frequent than in England, the United States, and Central Europe. The negroid likewise is rarely afflicted with ulcer. Such an anomaly may be explained only if we apply to diseases—particularly to chronic nonbacterial diseases—the constitutional element.

Notwithstanding the astonishing advances that have been made in the study of constitution, there is one underlying principle regarding human constitution which we believe has not been emphasized. That is, that constitution, particularly in relation to disease, must be considered from the point of view of the human race, or at most of the higher animals next to the human race. Hence experiments on animals to produce certain diseases of a nonbacterial nature, such as metabolic and hematopoietic diseases, do not meet with the desired results. Experimentally, certain pathologic lesions may be produced in the animal resembling those in the human, but the course of events of that pathologic lesion in the vast majority of cases shows such a

great variation from the course of a similar lesion in the human that the correlation of the experiment to human pathology becomes less and less apparent. Because of this even the most exact experiment sometimes suffers undue criticism. From the earliest historical time to our present highly civilized day, the tendency of the human race has been toward migration. As a result of his changes man has altered his being and has acquired certain characteristics which, on the surface, appear natural, but which are, nevertheless, alterations of an original pattern. The very fine distinction by Tandler that constitution means only that which one has never acquired, and that which one acquires is conditioned, is only relative. No one in the human race is constitutionally destined to have abnormal distribution of pigments in the skin or a sixth finger, but in the course of alteration of pattern such anomalies do result. These alterations occur sometimes when a particular race has to accommodate itself to an unfamiliar mode of living or to an unaccustomed climate. Burbank planted the seeds of different fruits and created a fruit common to them. In the course of that accomplishment, many characteristics that would almost signify freaks of nature necessarily resulted. In the simple growth of fruit, freaks are exceptional because the conditions for perfection are easily provided. However, in the complicated human race freaks in a pattern may and frequently do result because the course of accommodation is difficult. Such freaks may be of a somatic nature, they may be confined to an organ, or they may be spiritual in nature.

From the foregoing, the importance of the relation of constitution to disease in general becomes apparent. An understanding of the relation of the individual organs to constitution and the factors that influence the function of these organs has been made possible largely by the studies of Eppinger and Hess, Riedel, Kraus and Zondek, Tandler, Draper, and Brown.

The work of Eppinger and Hess regarding the relationship of a balance in the vegetative nervous system and its influence on function—even in the production of a definite disease—was described above. It was their work that furnished the impetus to

von Bergmann for the promulgation of his spasmogenic theory of peptic ulcer which re-fortified the vascular theory, then almost overthrown. The work of Riedel on the relation of the glands of internal secretion to general constitution is too well known to need elaboration. Since Riedel's contributions, a great deal of experimental work has been done in this field, chiefly with the suprarenals and thyroid. The interesting studies of G. A. Friedman have already been mentioned. The work of Crile regarding the suprarenals and thyroid, and their relation to the pathogenesis of peptic ulcer, has been so illuminating that this author now advocates partial excision of a suprarenal and partial thyroidectomy as a method of cure of peptic ulcer. Kraus and Zondek, basing their studies on the work of Jacques Loeb of the Rockefeller Institute regarding the exact calcium balance regulating the sympathicus and potassium greatly influencing the vagus, have shown that the autonomic, internal secretion, and electrolytic systems are closely allied. Kraus (as was stated above) named the combination of these the vegetative system, and demonstrated that a disturbance in any one of the three systems, depending on degree, generally sets up changes in the other two. In some individuals the changes are primarily in the autonomic nervous system, in others in the glands of internal secretion, in still others in the electrolytes.

The anatomical studies of Tandler led him to the conclusion that we cannot speak of "congenital constitutional" and "acquired constitutional" defects. Constitutional, literally, applies only to the characteristics that one carries from birth. Those that are acquired through environmental influences are conditioned defects. Tandler's division is not purely academic. It is our own conception, based on experience, that actual constitutional defects if not of a very severe nature are not as harmful or as apt to cause disease of certain organs as the conditioned defect. Organs with a genuine constitutional inferiority—for example a small heart, phthisical chest, or malpositioned teeth—may by proper environment or training not only attain a state of normal function, but may even become normal anatomically. On the other hand, the body or organs of an individual who was

born anatomically normal, may through environment, habit, or other exogenous influences, become inferior and through continued abuse become predisposed to disease. To illustrate, one born with a healthyheart may become afflicted with rheumatic fever and cripple his heart. From the anatomical standpoint, undoubtedly Tandler's conception is correct.

Of great importance regarding the relation of constitution to disease, are the studies of George Draper who described certain external features as indicative of certain constitutions and succeeded in demonstrating many examples where the external appearance of the individual is an indication of the disease to which that particular type is subject, or the disease with which he may happen to be afflicted. Draper describes the type predisposed to duodenal ulcer as an adult in the active, driving period of life, frequently excitable, easily worried, and restless under some mental or physical strain. Often the facies depicts this strain, as evidenced by horizontal furrows on each side of the mouth, a tense jaw, and flattened cheeks. The upper jaw is frequently somewhat narrow and the upper median incisors project over the two lateral incisors. The angle of the mandible tends toward the acute.

A recent experimental contribution, very important from the clinical standpoint, has been made by Wade Brown of the Rockefeller Institute. Through painstaking experimental studies on rabbits, he has demonstrated that three factors influence the pathogenesis of disease: (1) The size of the individual organ in relation to body size; (2) physicochemical changes in the blood, and (3) fluid tissue particularly of the lymph and lymph nodes.

Regarding the relationship of the individual organ to body weight, he found that in large rabbits the important internal organs are relatively small, whereas in small rabbits the individual organs, particularly those of internal secretion, are relatively large. The large animals with comparatively small organs when subjected to disease-producing experiments developed disease more readily and more often fatally than the small animals with comparatively large organs.

According to Brown, there are two phases of organic con-

stitution to consider—organ-body weight relationship and organ equilibrium. He found a seasonal ebb and flow in animal organisms comparable to that in plants subject to the influence of external conditions. The organ-body relationship and organ balance may differ in individuals by virtue of inheritance and may vary from month to month and year to year, in response to environmental influences with, however, a normal trend. The tendency in summer is toward a high positive organ balance with a predominant endocrine influence and vice versa in winter. The change from a summer to a winter status is accomplished by a rapid but continuous transition from the maximal level of July or August to a minimal level in November. The transition from winter to summer conditions is irregular and discontinuous, tending to reverse movement. These studies of Brown have verified the popular conception that the husky individual is more susceptible to infection than the thin, wiry individual. However, the reason why the husky individual succumbs more readily may be that in contradistinction to the frail individual, who by frequent minor infections vaccinates and revaccinates himself, he acquires disease without previously graded immunity. The findings of Brown explain the frequency of disease during certain seasons and why the reaction of individuals to disease differs in spring and fall. If one is afflicted in the transitional period from winter to spring, the course is apt to be drawn out and interrupted, whereas certain diseases acquired in the transitional period of fall to winter are less likely to be prolonged. This would explain in part why peptic ulcer symptoms recur with almost mathematical regularity during the spring and fall and are generally more protracted and not so quickly influenced by treatment in the spring.

The relation of constitution to disease has, of course, been utilized in the interpretation of the pathogenesis of peptic ulcer. It has long been known that the status of the individual plays a rôle (see Figs. 65–67). It has been accepted, almost as an incontrovertible fact, that the hypersthenic individual with a broad stomach who eats rapidly and pours his gastric contents in a hyperacid state into the duodenum causes repeated irritation

(reizustand, Siebeck) of the duodenum. If ulcer develops in such an individual because of the protracted irritation, it will develop on the duodenal side. In the asthenic individual, on the other hand, due to atony of the stomach, there is a delay in emptying with a tendency toward stagnation of food, causing irritation on the gastric side which, if persistent to the extent of causing the development of ulcer, will produce the ulcer on the gastric side. Some authors—indeed so important an authority as Hurst—are of the opinion that the status of the individual is,

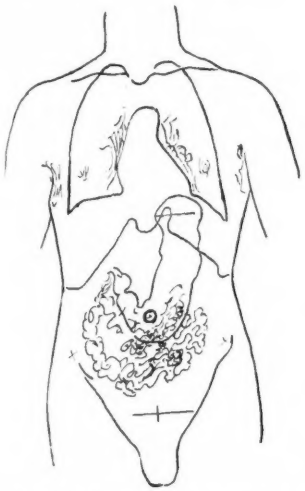

Fig. 65.—Constitutional sthenic habitus (Dr. R. Walter Mills).

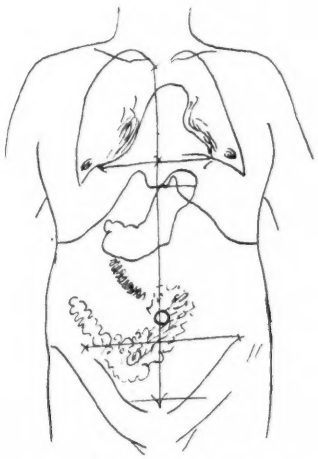

Fig. 66.—Constitutional hypersthenic habitus or apoplectic type.

in the majority of cases, the great deciding factor regarding the ulcer site. In a publication we, too, concurred in the opinion that the duodenal ulcer usually occurs in the hypersthenic individual and the gastric ulcer in the asthenic individual. We believed at that time (1913) that the hyperperistalsis and the rapid emptying of the stomach during the early part of digestion —two of the so-called "indirect roentgenographic signs" of duodenal ulcer—were actual precursors of the ulcer and indicated that the acid chyme was poured into the duodenum massively

and early. We also considered the roentgenographic manifestations of delay in emptying in the asthenic type a precursor of gastric ulcer.

Whereas it still seems to us that this conception is not wholly incorrect, clinical experience has since taught us that it should be somewhat modified. We have been impressed by the fact that with regard to the relation of status to disease, the constitutional and conditioned-constitutional status must be differentiated. The constitutional status (hypersthenic or asthenic)

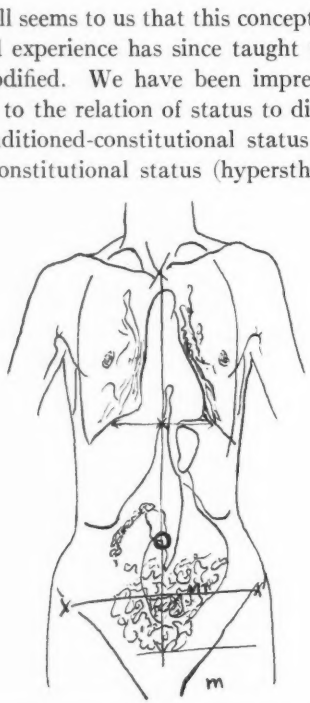

Fig. 67.—Constitutional asthenic habitus. Asthenia universalis congenita of Stiller (Dr. R. Walter Mills).

so long as there is no definite pathology in the organ will by virtue of accommodation and training succeed in preventing disease of the organ. To illustrate, the asthenic individual born with atonic abdominal viscera who suddenly develops functional symptoms from only a slight cause becomes over-attentive regarding his digestive organs—sometimes to a degree as to make him introspective, even neuropathic. By careful training most of these individuals escape actual organic disease. The consti-

tutional hypersthenic individual who develops symptoms of bloating and distress, due to quick and excessive eating, likewise heeds his symptoms and by training generally avoids organic disease. Of the two, the hypersthenic type with his naturally phlegmatic nature and over-confidence in health is more apt to ignore symptoms and so become afflicted with disease that is the result of abuse than is the asthenic one. *However, if either the asthenic or hypersthenic type of individual, due to some factor, does develop ulcer, the site of the lesion is not necessarily determined by status. The asthenic individual may have a duodenal ulcer and the hypersthenic may have a gastric ulcer.*

Fig. 68.—Conditioned asthenic habitus, showing a low stomach in a patient with a high transverse colon.

The individual with a conditioned status of the organs is one in whom the position of the organs was originally normal, but through abuse became altered without a change in external appearance. In the constitutionally asthenic individual the low stomach is really not a ptosed stomach and (as shown by Alvarez in this country and by Moody in England) is present in a large number of individuals without accompanying symptoms. The

conditioned asthenic individual, however, actually has a ptosed stomach (Figs. 68, 69). The organ is not only very low, but is much more atonic; the pylorus is equally low. The constitutional asthenic type has all the organs proportionately long. When one is a conditioned asthenic type he may alter the type of certain organs and not of the others, for example the stomach as just stated is low, but the colon or its flexures may be very little

Fig. 69.—Conditioned asthenic habitus, showing a high transverse colon in a patient with a low stomach. Same patient as in Fig. 68.

altered. One rarely encounters all the viscera proportionately low in the conditioned asthenic type or all the viscera high in an individual of conditioned hypersthenic type (Figs. 70, 71).

It seems to us that these findings may be explained on the following basis: The constitutionally asthenic individual can convert his stomach into a hypersthenic type by forcible feeding and rest in the treatment of his asthenia, and may eventually

reach a stage of overweight, or the overweight may occur during middle life—more often in women, but also in men—when the individual begins to gain weight out of proportion to the intake of food. Again, the constitutionally hypersthenic person may overdiet due to a desire to fit the body to a style, or because of an intercurrent disease, and lose so much fat that the support of the abdominal viscera is lost. The stomach becomes a condi-

Fig. 70.—Conditioned hypersthenic stomach. Showing the stomach above crest of ilium. The transverse colon is V-shaped below the crest of ilium.

tioned asthenic type. This malposition of the abdominal viscera may also be the result of the acquired pendulous abdomen with diastasis recti as a result of repeated pregnancies.

Regarding the conditioned status, we believe we are justified in going a step further and stating that even other diseases, like metabolic and hypertensive disturbances, more often occur in

the individual with an acquired or conditioned status. We know that overeating leads to diabetes, and we are all familiar with the susceptibility of the broad, hypersthenic individual to apoplexy. However, one born with the status apoplecticus often goes through life with normal blood vessels and not every individual who overeats has diabetes. When, however, through overeating an in-

Fig. 71.—Conditioned hypersthenic stomach. Showing the transverse colon V-shaped with the apex in the true pelvis. Same patient as in Fig. 70.

dividual alters his status, he may develop diabetes or overtax his vascular system and develop hypertension. The term "status apoplectus" in the conditioned sense is often as misleading as when, formerly, we spoke of the thin, flat-chested individual as the one most likely to develop tuberculosis, whereas in reality

pulmonary tuberculosis is far more often encountered in individuals whose lungs are in a normal chest.

That the transverse position of the stomach would predispose the duodenum to ulcer because of the gastric chyme is, of course, plausible, and would explain why in early youth if ulcer develops it usually occurs in the duodenum. During this period the position of the stomach is so high and transverse that in the first three or four years it is practically saddle shape, and up to ten years has the typical "cow-horn" shape.

The practical aspect of an appreciation of the constitutional factor in relation to disease is evidenced in the occurrence of peptic ulcer in several members of a family in direct blood relation—fathers and sons, brothers and sisters—and even in more distant relatives of a family. The familial tendency is, of course, not as outspoken as it is in certain other diseases, for instance rheumatic endocarditis. Some observers, who have not themselves encountered more than one case in any family, minimize the familial tendency or go so far as to deny it altogether. Others, like Bauer, Matthes, and Barker, who have paid a great deal of attention to the relation of constitution to disease in general and have closely observed the familial tendency of peptic ulcer, state that the familial tendency is an indisputable fact. We have personally encountered four brothers in one family afflicted with duodenal ulcer, three of whom were operated and one of whom had a gastric hemorrhage. In another family, we saw a father and son afflicted with peptic ulcer, and in still another there were three brothers who suffered from that disease. The conditioned status may run through some families because of an equal mode of living. Such a conditioned status may manifest itself in the body at large or in the individual organs. This conditioned status in certain families may be directly transplanted to future generations in whom it then becomes constitutional and is no longer conditioned. This again emphasizes the fact that in the minutest sense of the word nothing is constitutional; i other words, at one time some member of a previous generation, albeit remote, must have acquired the conditioned factor or factors that later emerged as a constitutional quality.

The constitutional viewpoint, surely, is very important in explaining the location of the ulcer. To understand this more completely, however, a brief discussion of the anatomical architecture of the stomach is indicated. The typical peptic ulcer usually exists in specified areas of the lesser curvature of the stomach and the duodenal ulcer, in the great majority of cases, on the lesser curvature of the first portion of the duodenum almost adjacent to the pylorus, occasionally on the greater curvature near the pylorus. Duodenal ulcer is rare in the second portion of the duodenum, and very seldom occurs in the third portion at its junction with the second portion. As far as the second portion is concerned, it is known that the ulcer occurs mostly in a part where there is either congenital diverticuli or some other mechanical hindrance. If the ulcer occurs in the third portion at its juncture with the second portion, it is likewise due to a mechanical hindrance causing stagnation. In these portions, one may state with a high degree of certainty that the tryptic factor, as Stuber pointed out, plays an additional rôle. The explanation for the prevailing occurrence of ulcer on the lesser curvature of the stomach and the first portion of the duodenum is difficult. The rôle played by the anatomical and functional conditions of the lesser curvature must be considered, not only from the standpoint of the blood and nerve supply, but also from that of musculature and Waldeyer's sulcus ventriculi.

VASCULAR SUPPLY

It is known that on the lesser curvature the blood vessels are scanty and terminal. Therefore, any injury to a vessel either from without or by thrombosis or infarction leads to local damage of the surrounding tissue which may become permanent.

NERVE SUPPLY

The lesser curvature is more actively innervated than any other part of the stomach and is therefore more sensitive, neurogenically. The vagus with its predominant motor fibers and only a minimum (about 10 per cent) inhibitory fibers on the pyloric sphincter, and the sympathicus with its predominant in-

hibitory fibers and a minimum (about 30 per cent) of motor fibers exert their influence through the lesser curvature. Hence, if any exogenous disturbance affects the autonomic nervous system of the stomach the most deleterious influence regarding motility is exercised on the lesser curvature. Moreover, there is on the lesser curvature near the cardia a specific musculature, structurally resembling the sino-auricular nodal center of the heart, from which motor impulses are directed, actually determining peristalsis of the stomach. The studies of Keith, Hoffmeister, Schutz, and E. Klein have contributed a great deal to our understanding of normal peristalsis of the stomach. They have shown experimentally that if some part of the lesser curvature is injured retroperistalsis instead of anastalsis results. This has a twofold significance. In the first place it explains why deep ulcers on the lesser curvature of the stomach and duodenal ulcers so frequently lead to vomiting and gastric retention without stenosis, and secondly it explains why excision of an ulcer on the lesser curvature leads to incessant vomiting so that jejunostomy must be resorted to so that the life of the patient may be saved. It was for this reason that this procedure had to be discontinued. The deep-seated penetrating ulcer or its excision so injures the conductivity of the nerves that anastalsis instead of peristalsis results.

MUSCULATURE

The musculature of the stomach consists of the muscularis propria and muscularis mucosa. The former has an outer layer of longitudinal fibers and an inner layer of circular fibers. The longitudinal fibers come down from the esophagus and run along the lesser curvature in a compact manner to the pylorus. These fibers are distributed very scantily along the fornix and lateral wall. On the greater curvature and pars pylorica, the longitudinal fibers are more defined and appear to be more compact. Most of them terminate in the sphincter of the pylorus, but some go over to the first portion of the duodenum. The circular fibers of the esophagus appear in strong bundles in the region of the cardia and in thick distribution at the lesser curvature until

they reach the pylorus where the strong pyloric ring is formed. Along the fornix and greater curvature these fibers are thinly distributed. The oblique fibers run from the cardia to the fornix (Fig. 72). They are found in no other part of the gastric tract. These form a muscular belt around the left side of the cardia

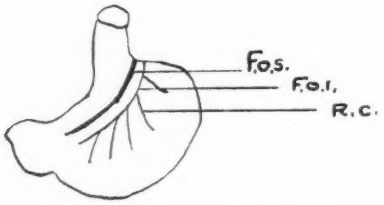

Fig. 72.—Schematic drawing of the stomach: *F.o.s.*, Fibrae obliquae pars superior: *F.o.i.*, fibrae obliquae pars inferior; *R.c.*, rami communicantes.

and separate to the anterior and posterior walls of the stomach, terminating in the antrum pylori. The function of these oblique fibers is, according to Rudolph Kauffman, to bring the upper part and the anterior and posterior walls of the stomach in the region of the lesser curvature near each other. The function of the

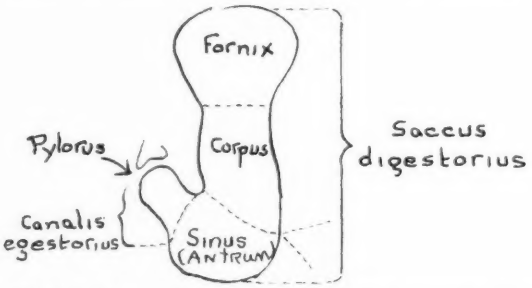

Fig. 73.—Division of stomach into two compartments according to its function.

lower bundle of oblique fibers is local contraction of the stomach identical with the intestinal segmentations. These upper and lower bundles of oblique fibers by their peculiar distribution form a connecting link between the pars pylorica and the groove of Retzius (Fig. 73) on the one hand, and the fornix on the

other. Liquid and solid food can thus pass through the groove from the esophagus to the pars pylorica and by means of retroperistalsis may pass from the sphincter pylorica toward the esophagus. The musculature of the stomach is thickest and strongest at the pylorus (3.5 mm.), less thick on the lesser curvature (1.5 mm.), and thinnest at the fornix (1 mm.; in certain parts 0.4 mm.).

The stomach may be divided into two definite compartments (Fig. 74), a vertical portion formed by the medium and external layers of the longitudinal bundle and by a superior loop of the inner layer, and a transverse portion formed by the transverse layers. The upper part of the fornix with its mus-

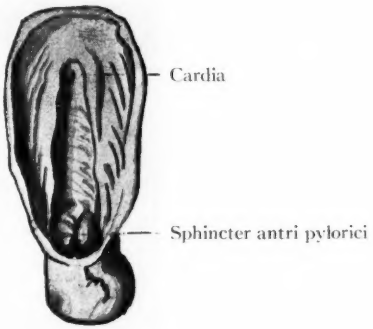

Fig. 74.—Retzius groove (or Magenstrasse of Waldeyer) formed by the upper horizontal part of fibrae obliquae along the lesser curvature of the stomach.

culature can be compared to the auricle of the heart; the pylorus and lesser curvature with their strong musculature to the ventricle of the heart. We hold with Aschoff, Waldeyer, Cole and others that the groove of Retzius has an important function in conjunction with the canalis egestorius, although it has not yet received the physiologic importance it deserves. With regard to the motor function of the stomach, according to the experiments of Cannon, Hofmeister, Schutz, Sick, Guntzner, and others the greater part of the work of the stomach is done by the region where the musculature is best developed, that is in the

pyloric part of the lesser curvature. Reeder, Rosenthal, Kassell, and Cole have shown cinematographically and by serial roentgenography that the canalis egestorius and the lesser curvature of the entire region of the saccus digestorius work harmoniously and are more active than the fornix (Fig. 73).

We have dwelled somewhat in detail on the specialized studies of the anatomy of the stomach pertaining to muscular function because it seems to us that there is a direct relationship between the development of the musculature and the formation as well as progression of an ulcer. The mechanical demand, which we discussed in detail in 1913, that is exerted almost exclusively on the antrum pylorum and the groove along the lesser curvature largely explains the predisposition of these parts to ulcer.

LOCAL TISSUE REACTION

The fact that only certain individuals with exactly the same blood supply, innervation and musculature develop ulcers while the great majority do not, would indicate that some other factor, which must unfortunately still be called *x*, exists to account for the formation of the ulcer. In some, this so-called "*x* factor" may be an erosion which, if it happens to occur in a part of the stomach where function is excessive and the anatomical relations do not favor healing, may progress to a deep, peptic ulcer. Such are the cases where the ulcer—like the toxic ulcer of Bolton—can be traced from its acute to its chronic state. It is probable, also, that some of the ulcers secondary to chronic appendicitis or chronic gallbladder disease originate as erosions, or that they are either of a toxic or infectious nature. This mild gastric erosion secondary to appendicular or gallbladder disease seems to us of great importance clinically. It is well known how frequently gastric or duodenal ulcer symptoms persist without any roentgenologic or even chemical evidence of disturbed gastric secretion or occult blood, but with positive evidence of appendicular disease, less often gallbladder disease. In such cases, one cannot exclude a small gastric erosion as the cause of the symptoms. This is not without practical value because where original chronic appendicitis or gallbladder disease gives rise to gastric

or duodenal ulcer symptoms, the removal of the diseased appendix or the diseased gallbladder should be urged.

Again, the predisposing factor *x* may be wholly speculative. When we attribute it to a disturbance in one of the three branches of the vegetative system (autonomic nerves, organs of internal secretion, or electrolytes) we feel that the local tissue reaction in certain individuals, even in a number of individuals of one family, is also of great importance, and that the susceptibility of this local tissue to disease is out of proportion to the rest of the stomach and of the body. In some individuals there may be a localized spasmophilic tendency confined to the stomach which predisposes the most sensitive areas to persistent spasm and eventual ulcer formation. The persistent spasm gives rise to symptoms of functional disturbance without demonstrable ulcer long before the occurrence of the actual ulcer. Also, the status lymphaticus associated with gastric ulcer, according to some authors, need not be generalized, but may be confined to the stomach thus favoring local invasion by infection. Intestinal epithelium has been found upon the lesser curvature which, if exposed to gastric secretions, is digested. On the basis of such findings by Schmidt (Adolph), Lange, Faber, and others, Schutze advances the theory that ulcer of the stomach occurs in parts of the stomach where the mucosa happens to be lined with intestinal epithelium. If such epithelial cells are present in individuals with achylia no ulcer results, but in the presence of acid ulcer does occur. With regard to the rare occurrence of ulcer on the greater curvature, it is probably the purely mechanical factor that plays the greatest rôle.

CONCLUSIONS

1. No single cause can be considered solely responsible for peptic ulcer. Despite experimental and even clinical controversy, the vascular theory of Virchow and Cohnheim is still very important as an explanation of the direct cause of peptic ulcer. The vascular insult, however, need not, and indeed cannot be traced in the great majority of cases to direct vascular disease or to infarction. Generally it is the spasm of the vessels in the vicinity of an ulcer that forms the basis of the disturbed nutri-

tion of the part of the mucosa supplied by the vessels that eventually has led to the formation of the ulcer. The mechanical theory of Aschoff, and the recently revived acidity theory, are likewise important as etiologic factors. Most of these causes, however, can at best be considered direct. The predisposing indirect cause must be traced to constitution.

2. The constitutional factor is of two types: The born characteristica (truly constitutional) and conditioned characteristica (conditioned constitutional). The constitutional factor need not be, and in most cases is not, evidenced by external appearance. It resides chiefly in the response of the stomach proper to exogenous and even to endogenous influences. Such exogenous and endogenous influences are more apt to cause an ulcer in a stomach that has been altered in status by conditional influences than in a stomach of constitutionally abnormal status. An organ that is constitutionally inferior is spared by necessity, or by some compensatory mechanism provided in the body by nature to take up the function of the defective organ. However, when an organ is altered by circumstances, accommodation is at best very slow. Repeated irritation may cause disturbed accommodation to the point of permanent injury.

3. The factors that tend to alter the type of a stomach are numerous. Not the least important of these is an imbalance in the vegetative nervous system. Certain occupations, too, which cause constant irritation of the stomach, either by direct pressure against the organ or by an injurious mode of living, are not to be overlooked.

4. Whether an ulcer is to be duodenal or gastric would seem to be determined as follows: If a hypersthenic stomach is acquired and an ulcer occurs it is generally duodenal; if an asthenic stomach is acquired and an ulcer forms it is usually gastric.

5. The reason why the ulcer is confined to certain locations on the lesser curvature may be found in the anatomical architecture (blood supply, musculature, innervation, and the area of mucous membrane) of the region.

6. The occurrence of peptic ulcer in some individuals and not in others with an identical architecture of the stomach is as

yet not entirely satisfactorily explained. The cause is still unknown although, undoubtedly local tissue reaction is influential in determining the exact site of the ulcer in certain cases. In rare instances, this local tissue reaction may be the result of implanted intestinal epithelium, or it may be due to excessive lymph follicles, either accompanying a general status lymphaticus or the remains thereof.

BIBLIOGRAPHY

Aschoff, L.: Lectures on Pathology, New York, 1924, Paul B. Hoeber.

Balint, R.: Ulcus problem in Saurebasen Gleichgewicht, Berlin, 1927.

Brown, Wade H.: Arch. Int. Med. Vol., 45, No. 5, pp. 625–662, November, 1929.

Buchner, Franz: Magensaft. Gastritis und Peptisches Geschwur, Klin. Woch., 9, Jhg. No. 1, 1930, pp. 1–5.

Cheney, Garnett: Jour. Amer. Med. Assoc., vol. 93, No. 26, p. 2021, 1929.

Deaver, John B., and Burden, Verne G.: Surg. Clin. N. Amer., vol. 9, No. 5, October, 1929.

Draper, George: Disease and the Man, London, Kegan Paul, 1930.

Durante, L.: Surg., Gynec., and Obst., 1916, vol. 22, pp. 399–406.

Friedman, G. A.: Jour. Med. Res., vol. 32, No. 2, May, 1915.

Hartman, H. R., and Rivers, Andrew, B.: Arch. Int. Med., September, 1929, vol. 44, pp. 314–338.

Hauser, G.: Peptische Schadigungen des Magens und Darms in Henke-Lubarsch, Bd. 4, I Teil, Julius Springer, 1926.

Held, I. W., and Gross, M. H.: Ulcus Ventriculi, Arch. Int. Med., vol. xiii, pp. 426–470, March, 1914.

Held, I. W., and Gross, M. H.: Roentgen Rays as an Aid in Diagnosis of Ulcus Ventriculi, Amer. Jour. Med. Sci., No. 5, vol. clv, p. 713, May, 1918.

Hitzenberger, K., and Reich, L.: Wien. Arch. Inn. Med., vol. 7, p. 309, 1924.

Hurst, Arthur F., and Stewart, Matthew J.: Gastric and Duodenal Ulcer, Oxford Univ. Press, 1929.

Katsch, G.: Handbuch der Innern Med., Mohr and Staehelin, 2d ed., vol. 3, Part 1.

Klein, E.: Ann. of Surg., July, 1929, p. 65; Arch. of Surg., vol. 12, pp. 571–590, February, 1926.

Konjetzny, G. E.: Arch. f. Klin. Chir., 1924, cxxix, 139.

Konjetzny G. E., and Puhl, H.: Med. Klin., 1927, xxiii, 986, 1025, and 1063.

Lorber, L.: Bioch. Ztschr., vol. 148, 1924, p. 41.

Mann, F. C.: Trans. of Assoc. Amer. Phys., vol. 142, 1927, pp. 224–227.

Mann, F. C., and Williamson, C. S.: Ann. of Surg., vol. 77, 1923.

Meyer, Kurt: Zur pharmakologische Analysen der Anaphylaktischer Reaktion, Zeit. f. Immunitätsforsch. u. exper. Therap., 72, 270, July, 1929.

Palmer, W. L.: Mechanism of Pain in Gastric and Duodenal Ulcer, Arch. Int. Med., 39, p. 109, 1927.

Rosenow, E. C.: Jour. Inf. Dis., 1916, xix, 333 and 1923, xxxiii, p. 248.
Siebeck: Deut. med. Woch., 55, Jhg. 42, 43, October, 1929.
Stuber, B.: Klin. Physiol., 2d Teil, p. 223, München, 1927.
Tandler, J.: Konstitution and Rassenhygiene, Zeit. f. angewandte, Anat. u. Konstitutionlehre, Bd. 1 S 11, 1913.
von Bergmann, Gustav: Mohr und Staehelin's Handbuch d. inn. Med., 2d ed., Vol. 3, Part 1, Berlin, 1926.
Zondek, S. G.: Die Elektrolyte, Berlin, Julius Springer, 1927.

CLINIC OF DR. WINFIELD SCOTT PUGH

CITY HOSPITAL

TUBERCULOSIS OF THE KIDNEY IN CHILDHOOD

IN a large institution such as this we are constantly seeing rare and unusual cases, but I carefully exclude them from clinical lectures believing that such are more confusing than instructive. Not long ago we listened to a teacher of renown, discussing with his class the possible pathologic entities in the right iliac fossa. The learned gentleman in this instance mentioned everything that might be found in the said area except that by no means rara avis, an acute appendix, the operative finding.

Following this introductory you will probably be not a little surprised to have us present a case of tuberculosis of the kidney in childhood. Mayhap someone is wondering what kind of apology we will make. I can assure you there will be none. Perhaps, then, says my young friend here, you will tell us something of its frequency and importance. Really, gentlemen, it occupies a place in urology of much less prominence than it deserves.

INCIDENCE

Tuberculosis of the kidney in children is so seldom reported (note that last word) that the disease is regarded as rare. We might go a bit farther and say it receives so little recognition that it is seldom looked for. Not long ago one prominent surgeon told us that tuberculosis of the kidney was comparatively uncommon before the age of eighteen years; but thought, however, that the disease was much more frequent than is generally appreciated. We can whole-heartedly endorse this statement as it coincides so well with our own findings.

In 1082 cases of renal tuberculosis reported by different writers in which the age was stated only six or a little more than 5/10 of 1 per cent occurred in children under eleven years of age. Schwartz stated that in an extensive autopsy experience he has found renal tuberculosis in children in the proportion of about one in five hundred examinations. One observer reports that he found advanced renal tuberculosis in the necropsy on a child one year old. In this case while the lung was involved there was apparently no general dissemination of the disease. Of 47 cases of surgical renal tuberculosis in children reported by a large hospital for children, 4 were under three years of age, 8 others between three and six, and 9 from six to eleven years.

Frisch mentions one group of 162 autopsy records for pulmonary tuberculosis in which there was one kidney involved and in this collection we find 30 renal organs affected in children under ten years of age. I am not quite sure, but I think it was the Pazman institution that showed records of 33 children under four years of age with pulmonary disease and in whom renal tuberculosis was found in fourteen. Another record shows kidney involvement in 16.2 per cent of three hundred children who died of pulmonary tuberculosis. Still a later record finds the kidney involved in 33 per cent of one hundred tuberculous children. Certainly a very high incidence, if correct. Kerley is one of the few authors emphasizing the importance of renal tuberculosis in children and he states that it has occurred in 25 per cent of his infantile cases of tuberculosis.

The kidney epithelium seems to provide a soil well adapted to the growth and rapid multiplication of the tubercle bacillus. This being so, why do we not have more reported cases in children? One reason is because in the preadolescent stage the disease becomes so rapidly diffused that the kidney soon forms part of the picture of a generalized tuberculosis. Another reason is lack of persistence in definitely placing the responsibility for the renal infections in childhood. We have been convinced that many of the obscure and persistent pyurias of infancy in childhood are of tuberculous origin. For our persistence, reward has crowned the effort by detecting the tubercle bacillus in 5 hazy cases. Bi-

lateral infection in childhood is noted in about 28 per cent, being practically the same as that of adults.

PATHOLOGY

Information as to the exact pathology of renal tuberculosis in infancy is rather meager. Kerley tells us that the involvement is of the miliary type with the tubercles scattered over the surface of the kidney, a few being noted within its substance. According to Holt, these miliary tubercles give rise to no symptoms and are of no clinical importance, while larger deposits are exceedingly rare in early life. It is difficult for us to reconcile this latter statement with our own findings.

Just a few remarks on our own limited observations of the morbid anatomy in this disease. It would seem to us that in children we have as in adults three very different pictures in the morbid anatomy and histology as follows:

(*a*) Primary closed parenchymatous tubercular nephritis.

(*b*) Primary open tuberculous pyelonephritis.

(*c*) A combination of the foregoing.

When first seen the lesions may vary from an almost microscopical tubercle to a complete disintegration of the renal substance. The small tubercles often produce no symptoms whatever and are discovered accidentally at the postmortem. We have seen cases in the necropsy rooms of the large European hospitals where a kidney was almost completely destroyed, the history showing no evidence of urinary symptoms or findings. It is true in these later cases the ureter was entirely closed and the kidney a mere caseous sac.

The chief reason why little is known regarding the pathology in tuberculosis of the kidney during childhood is not difficult to understand. Tuberculosis of the kidney is seldom, if ever, a primary disease and as I have told you previously when it occurs in the very young, it becomes so rapidly diffused that it forms merely part of a generalized process. The form of the disease most commonly met with is that of the tuberculous pyelonephritis.

SYMPTOMS

In all the cases we have thus far seen the symptoms and signs were definitely those of a pyelitis. Pyelitis, you say! Oh, what a word, and as a result almost every kidney case in childhood is so labeled. There are other features also to be discussed later. One of the great misfortunes of the age is our unconscious tendency to group most cases as coming within our own particular perview. Unfortunately this dims our perspective considerably and may get us into much trouble. Preserve an open mind and it will keep you out of the quagmire.

It has always been my policy not to think of any one organ but to try to get a general lineup of the patient first. If this is an error it certainly is in the right direction. Therefore we probably note at first glance that our patient is a little below par, there is a history of loss in weight and strength. If questioned, the mother will tell us the child is frequently hot in the early evening and sweats somewhat at night. We then call in that dear old stand-by, the internist, and he deftly goes over the patient's chest and abdomen, locating with his sensitive fingers, scattered areas of dulness in the pulmonary region. In running down over the abdomen he may note tenderness of the renal area, or elicit a mass. The latter is unusual, but if found commonly means the little one is due soon to be transferred from the M. D. to the D. D. The internist will also supplement his examination with one made by the roentgenologist, and this cooperation is most valuable.

Now, coming to the urinary ways, what signs and symptoms have we here? Various authors tell us they look for frequency, urgency, and incontinence of urine with at times hematuria. Of what are the foregoing diagnostic? Absolutely nothing, they are simply nature's signals calling our attention to the urinary tract. It is a symbolic way of saying awaken brother and do a complete urological examination. This means a cystoscopy, functional tests, and urograms. Here is a definite problem in ratiocination. Unfortunately we have no Philo Vance to help us. You will say the parents are sure to object to this. Aye, I know it too well. Simply tell the parents the symptoms above

quoted, suggest a urinary disease, but that it may be located anywhere from the kidney down to the prepuce. There is no objection today to a bronchoscopy or a spinal puncture in children. The physician must teach the parents that urological examinations are just as necessary as in no other way can the disease be tracked to its lair.

I hope you will be patient with me just a moment if I digress in an effort to drive home the necessity for cystoscopy in children. In a series of five hundred consecutive urological examinations in children the following were found:

Pyelonephritis	320
Hydronephrosis	10
Pyonephrosis	12
Tuberculosis	4
Renal calculi	7
Ureteral	3
Perinephritic abscess	3
Polycystic kidney	1
Horseshoe kidney	2
Prolapsed kidney	1
Absent kidney	1

Not to mention many lesions of the lower urinary tract.

One gentleman has just been heard to say what of a voided specimen of urine, is it not of value? No, it is not of much value. If there are tubercle bacilli in it, we do not know where they come from. For a cystoscopy in a child one may use general, spinal, or caudal anesthesia. When a Number 12 Charrière cystoscope is introduced we may or may not find ulceration of the bladder in or around the ureters or a diffuse cystitis. Cystitis is truly a scapegoat and is never a real pathologic entity. By that I mean it is always part of another process. After inspecting the bladder, our Number 5 catheters are passed up to each kidney pelvis.

It is always well that our little patient be given water before the examination so that kidney specimens of urine are more readily obtained. The cystoscope is now withdrawn and the catheters left in place. The ends of our catheters drip into sterile test tubes and kidney urines are secured. A liberal sample is always advisable. Following this, functional tests are made

with phenolsulphonphthalein as in adults, and our urograms then taken, the pelvis being injected with 12 per cent sodium iodide. Shall we or shall we not do a double pyelogram? I should advise it by all means. Some teachers still hold that pyelograms should not be made in the presence of possible renal tuberculosis. This is care run rampant, and may defeat the diagnosis.

Now that specimens of kidney urine are obtained, they must be examined by concentration methods for the presence of Bacillus tuberculosis. Do not feel badly if it is not found at once. Guinea-pigs should be inoculated with the first specimen. Several years ago Bloch reported that tubercle bacilli were found sooner if the glands around the point where the guinea-pig was inoculated were bruised. I can simply say we would not depend too much on that.

In connection with what we have just said I want to again emphasize strongly the fact that we have formed the habit of suspecting tuberculosis in the persistent pyurias of childhood.

CASE REPORT

F. G., age seven years, white. The daughter of an employee of the Department of Sanitation, whose history is briefly as follows:

The father states his daughter has always been well up until six months ago when it was noticed that she was frequently feverish and her urine quite milky in appearance. He thinks also that his little girl has lost quite a little in weight and strength. The patient has been under the care of a local physician who examined the urine and made the usual diagnosis of pyelitis. In the last few months our little patient has been quite thoroughly dosed with urinary antiseptics to no avail.

You will note the child is decidedly pale and shows every evidence of having lost weight and strength to a considerable extent. In my general examination I thought I detected a right apical lesion in the lung. The medical staff went me one better and found both lungs involved, suggesting also there was probably a dissemination process. The eye man thinks there is probably tubercular involvement in the choroid of the left side. Our examination further shows us that there is an evening rise of temperature reaching 101 to 102 F., and that it drops in the morning, but never quite reaches normal. Coming to the urinary tract we note there is frequency of urination about every half hour during the day with pyuria and slight pain over the left renal region. I am not sure of a mass near this kidney but it is certainly very suspicious.

Cystoscopical examination under general anesthesia shows a slight general engorgement of the bladder most marked near the left ureter, below and in front of which there is apparent superficial ulceration. The bladder does

not appear to be distorted in any way. You know some of our well-known students have said that the bladder in renal tuberculosis reveals a picture corresponding to three distinct periods, that is:

1. The primary stage.
2. The secondary stage.
3. The tertiary or complete destructive stage.

This may be true but we do not feel that there is as yet enough clinical data at hand in these cases of childhood to substantiate it. The bladder, even when it is not contracted, seems irritable and will hold little fluid. Again

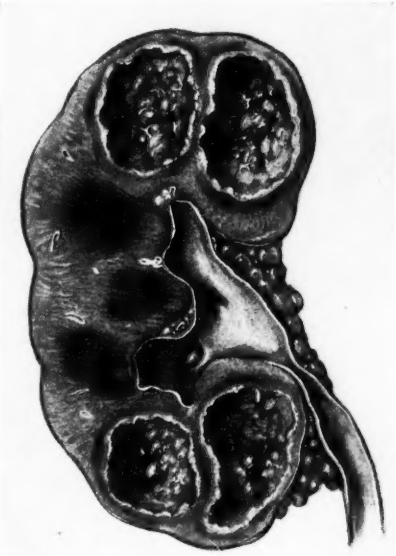

Fig. 75.—Specimen of a closed tuberculosis in upper and lower poles of child's kidney.

one or both ureters may be retracted giving the bladder a tentlike appearance on the side of the involved kidney. Undoubtedly if such ureters could be palpated per vaginum as we do in the adults they would be found quite rigid.

The urine specimens from both kidneys were at first negative for tubercle bacilli but on the second examination they were found in the specimen from the left side. Kidney function on the left was indeed quite feeble and the dye did not appear until after about fifteen minutes, while that of the opposite side was normal. Several tests of the right kidney urine were negative for tubercle bacilli, but the pathologist tells me there is much glandular enlargement in one of the guinea-pigs.

Briefly the above data are sufficient to convince us that we have an involvement of both lungs and kidneys by the Koch bacillus. The pyelogram of the left side, while not typical of tuberculosis, shows marked disease. As there was a little difference of opinion about double pyelograms in this case the right was taken separately and shows nothing suspicious.

Fig. 76.—An apparently normal pyelogram of child. Tubercular lesions later found in upper and lower poles.

PROGNOSIS

The outlook in all of these cases is extremely grave and at the very best one must be exceedingly guarded in discussing any possibility of recovery.

TREATMENT

As you undoubtedly know, there is considerable discussion among experienced physicians as to whether renal tuberculosis is a medical or surgical condition. As regards adults I admit the question is still a little hazy in my mind. In infancy and childhood, if we could say definitely this lesion is limited to one

kidney, surgery would be the answer. As it is practically never a localized condition we have a manifestation of disease that is decidedly best handled by medical measures.

In the disease under discussion I am becoming more and more convinced with the value of rest, good food, cold fresh air, heliotherapy, diathermy, hydrotherapy, and tuberculin. Treatment alone is a big subject, but briefly it is as follows:

1. All cases should be hospitalized and given plenty of rest. Kellogg says the latter reduces catabolic processes and lessens the excretory work of the kidneys. The essential phases of the diet according to Martin are the furnishing of a well-balanced ration affording maximum nourishment, yet imposing minimum work of elimination by the kidneys.

2. The supplying of foods rich in calcium and iron salts.

3. The furnishing of sufficient bulk to avoid intestinal stasis with the resulting auto-intoxication.

Real sunlight must be given in abundance; cover up the face if necessary, but let the body get as black as possible. Diathermy is of value in relieving the kidney and vesical pains if applied locally. Hot and cold douche baths, sprays, etc., are valuable tonics. Do not forget tuberculin, as Dillingham has reported 50 cases cured by its judicious use. Locally to the bladder, mild irrigations of dilute potassium permanganate are helpful and ulcers may be fulgurated superficially. Where there is great disturbance at night due to frequent urination an indwelling catheter will ofttimes be found of value, provided there are no ulcerations in the bladder neck.

In closing, just let me say that even though you do not actually cure, there will be much surprise at the improvement attained by the use of a combination of the remedies just advised.

CLINIC OF DR. CONNIE M. GUION

CORNELL UNIVERSITY MEDICAL COLLEGE

THE TREATMENT OF DISEASES OF THE THYROID GLAND

IN discussing the treatment of any disease it is essential that the nomenclature used be clearly understood. In reviewing the standard text-books and the current literature I found that the same pathologic change in the thyroid gland is described under varied diagnostic terms. For example, the enlargement of the gland that occurs at puberty is called "colloid goiter," "simple goiter," "adolescent goiter," etc. Graves' disease is described as hyperthyroidism, thyrotoxicosis, etc. Therefore the first problem that confronted me in the study of diseases of the thyroid gland was the selection of a classification. The one chosen follows closely the suggestions made to me by David Marine.

CLASSIFICATION

Thyroid insufficiencies:
- Simple goiter
  - Without symptoms.
  - With symptoms.
  - With adenoma.
- Hypothyroidism
  - Without goiter.
  - With goiter.
- Myxedema.
- Cretinism.

Graves' disease:
- Acute:
  - Primary.
  - Secondary.
- Chronic:
  - Primary.
  - Secondary (hyperthyroidism, dysthyroidism, thyrotoxicosis, toxic adenoma, etc.).

Malignant tumors:
Carcinoma.
Sarcoma.
Thyroiditis.

SIMPLE GOITER

By simple goiter is meant the uniformly enlarged, rather soft thyroid gland that occurs particularly at puberty and through the child-bearing period. It affects girls especially and is often periodically enlarged during menstruation, pregnancy, and lactation in order to meet the increased demand on the thyroid gland at these sexual crises.

As a rule there are no symptoms in the early cases. The patient seeks the advice of the doctor solely because of the goiter. The only physical sign is the enlarged thyroid gland. The basal metabolic rate is usually normal.

If the size of the gland becomes sufficiently large to compress the trachea or impinge on the recurrent laryngeal or the sympathetic nerve or if it becomes substernal there are pressure symptoms such as choking sensations, dyspnea, pain, hoarseness, cough, oculopupillary changes, etc. At this stage the gland is usually asymmetrical and firmer, due to the formation of adenomas, hemorrhages, fibrosis, and calcareous deposits. It is very important to emphasize these secondary changes because it may be possible to prevent them by early treatment of simple goiter. The basal metabolic rate usually remains normal, but it may be decreased.

Simple goiter with pressure symptoms must be distinguished from cases of autonomic imbalance with a globus hystericus. Each group may complain of the same symptoms, but the latter has no goiter.

If the cause for the deficiency of iodine is removed (*e. g.*, after puberty, pregnancy, lactation, etc.) a certain per cent of early cases may undergo spontaneous evolution. However, if the deficiency of iodine persists the secondary changes referred to above usually occur. If treatment is instituted early before these changes take place and is continued over a sufficiently long time excellent results may be obtained. After the secondary changes occur, medical treatment accomplishes little in most

cases. It takes at least one year before the effect of the medication should be judged.

Treatment of Simple Goiter.—*Prophylaxis.*—David Marine[1] states that 1 mg. or possibly less of iodine daily will ordinarily prevent simple goiter and its use is fraught with no danger. He advises that this dosage be given during pregnancy and lactation except in women with secondary adenomatous changes in the thyroid gland and with Graves' disease. In children with goitrous parents this treatment should be instituted early and continued through puberty.

The *treatment* of simple goiter should be started as soon as the enlargement of the thyroid gland becomes evident. David Marine[1] advises giving standard U. S. P. desiccated thyroid extract 0.1 to 0.2 Gm. (grain 1.5 to 3) daily for two weeks. If there is no evidence of thyroid intoxication in terms of an accelerated pulse, loss of weight, nervousness, etc., this dosage may be repeated under observation at weekly intervals. After an intermission of one or two weeks without any medication 25 to 50 mg. (grain 0.4 to 0.8) of iodine may be given daily for two weeks. This routine should be repeated every four months for one year at least and longer if the patient continues to improve.

Older patients may cooperate more satisfactorily when they are given the iodine daily in doses of 1 mg. over a protracted period. Such cases should be observed every two to four weeks.

The compound of iodine prescribed is immaterial so long as the dose of available iodine is correct. The following are the common medicinal agents used, with the iodine content given. It is worthy of note what a wide variation there is in the iodine available in the usual prescribed doses of these substances.

MEDICINAL AGENTS IN SIMPLE GOITER

1. Lugol's solution (liquor iodi compositus):
   1 cc. or 15 min. contains 130 mg. or gr. 2.
   1 min. contains 8.6 mg. of free iodine or gr. 0.14.
2. Ferrous iodide pill (pilula ferri iodidi):
   Gr. 1 contains 50 mg. or gr. 0.8 iodine.

[1] Marine: Iodine in the Treatment of Diseases of the Thyroid Gland, Medicine, vol. vi, p. 127, 1927.

3. Syrup ferrous iodide (syrupus ferri iodidi):
   1 cc. or 15 min. contains 40 mg. or gr. 0.6 iodine.
   1 min. contains 3 mg. or gr. 0.04 of iodine.
4. Syrup hydriodic acid (syrupus acidi hydriodici):
   1 cc. or 15 min. contains 13 mg. or gr. 0.2 of iodine.
   1 min. contains 0.86 mg. or gr. 0.014 of iodine.
5. Sodium iodide (sodii iodidum) gr. 1 contains 54 mg. or gr. 0.9 of iodine.
6. Potassium iodide (potassii iodidum) gr. 1 contains 50 mg. or gr. 0.8 of iodine.
7. Iodostarin tablets (gr. iv standard) contain 125 mg. or gr. 2 of iodine.
8. Thyroid extract, desiccated (thyroideum siccum U. S. P.), contains 0.017 to 0.23 per cent of iodine.

It is important to know that patients taking iodine often return at the end of a week, complaining of being worse. The thyroid gland is painful and has grown larger and harder. This is due to the accumulation of colloid subsequent to iodine administration. It lasts about a week and gradually decreases and is in no way deleterious, but is an indication that the use of iodine has been too large and it may be prevented by giving small initial doses.

There are, however, untoward effects that are very serious, which are seen often enough to make it seem necessary to emphasize the contraindication in using iodine. The routine established by Plummer and Boothby of giving daily thirty to forty-five drops of Lugol's solution as a preoperative measure in Graves' disease has set the fashion for using Lugol's solution indiscriminately in large doses over indefinite periods in all types of goiter. The situation is the more serious because those cases in which prolonged use is most harmful improve so decidedly during the first ten days to two weeks, that the inexperienced are encouraged to continue medication. This is illustrated in the discussion of Graves' disease.

During and after the menopause women with simple goiters of long standing are susceptible to iodine. By large, prolonged dosage a thyrotoxicosis may be precipitated that will not cease immediately on the withdrawal of the drug and may offer the usual problem of thyroid intoxication.

In simple goiters with adenomas the prolonged use of iodine may precipitate serious results. There may not be any evidence

of the adenoma before treatment, but after ten days with careful palpation one or more adenomas may be differentiated. If the iodine is continued, symptoms of thyrotoxicosis may develop which may last several weeks after the medication is withdrawn and in some cases they can be controlled only by an adenectomy. Boothby advises against the use of iodine in all such patients over twenty-five years of age. David Marine[1] states that all unfavorable reactions can be avoided by observing the rule of using not more than *10 mgs. of iodine per day for not longer than one month*, or *1 mg. a day for continuous use.* I have found this rule holds good.

x-Ray therapy has no place in the treatment of simple goiter. Surgery in early cases of simple goiter or in the adolescent child is rarely justified because iodine medication gives satisfactory results. In those cases with secondary changes in a large goiter, surgery is the only measure that offers any promise of reducing the size of the mass.

HYPOTHYROIDISM

By this term is meant a very common syndrome seen chiefly in children before the age of puberty and in women approaching or during the menopause. In both the basal metabolic rate is below normal, the pulse is slow, the blood pressure is low, the skin is pale and dry; they are nervous and irritable and have frequent headaches. They have very little endurance, they never feel quite well and they have frequent infections. They may or may not have an enlargement of the thyroid gland.

The children are usually poorly developed and under nourished, though they may be obese; they have poor appetites, are constipated and often have enuresis. The adults never feel quite well under ordinary circumstances and cannot carry responsibilities without collapsing. On the other hand, they are often quite well on a holiday. They have variable symptoms—on one visit they may complain of pains that affect all the joints of the body and are fleeting in character. On another day the pain may be abdominal and simulate appendicitis, cholecystitis,

[1] Marine: Iodine in the Treatment of Diseases of the Thyroid Gland, Medicine, vol. vi, p. 127, February 19, 1927.

etc., so characteristically that an operation may be advised. Again the symptoms may be urinary, such as nocturia, polyuria, dysuria, burning, oliguria, incontinence, and the urine may show albumin, casts, and a high percentage of bladder cells. A cystoscopic examination may show small ulcers, which recur after all types of local treatment.

David Marine[1] believes that this entire syndrome may be due primarily to a disturbance of the suprarenal gland and secondarily to the thyroid gland. We should bear this in mind in any investigation.

The children seem to respond well to the early administration of thyroid extract. The dosage depends on the basal metabolic rate and varies between 1/10 to $\frac{1}{2}$ grain (6 to 30 mg.) of the desiccated extract of thyroid (U. S. P.) three times a day for two weeks. An effort is then made to determine the optimum dose for the patient based on the general condition, the weight and pulse and basal metabolic rate determined every two to four weeks until it approaches as nearly normal as possible. Most of these children require $\frac{1}{2}$ to $\frac{3}{4}$ grain daily until after adolescence is well established.

The adults do not react as satisfactorily as the children. The same type of treatment is used, starting with the thyroid extract in doses of $\frac{1}{4}$ to $\frac{1}{2}$ grain (15 to 30 mg.). To patients who show no improvement with thyroid extract I have given adrenal residue, such as the glyadrenal pills of Schieffelin (MV or X). Some of them have been distinctly benefited as shown by the alleviation of their symptoms and the rise in basal metabolic rate, blood pressure, and pulse rate.

MYXEDEMA

The clinical picture of this disease needs no description here, but the fatal cases, due to treatment, make it wise to emphasize the caution necessary in the administration of thyroid extract. It must be remembered that the cardiac muscle is in poor tone and that the metabolism must not be increased too rapidly and overburden the heart. It is better to give smaller doses of thy-

[1] Personal communication.

roid over longer periods. I begin with a daily dose of desiccated thyroid extract 3 to 6 grains depending upon the condition of the patient's heart muscle and kidney function and basal metabolic rate. This dose is continued for at least a week, since the effect of thyroid medication does not manifest itself for about seven days. Daily observation should be made on the condition of the heart, the pulse rate, temperature, weight, and kidney function. If no untoward results occur, the dosage is increased to 6 to 9 grains daily for another week. By the end of the second week there should be a marked increase in the pulse rate, a rise in temperature, a loss of weight, and a rise in basal metabolism. As the full effect of these large doses of thyroid is not evident for another seven to ten days, it is wise to reduce the dosage at the end of the second week to 3 to 6 grains. Observation should be continued until the basal metabolic rate, the pulse rate, and temperature are brought as near to normal as is attainable and continue the optimum dosage indefinitely. David Marine[1] advises the use of iodine 10 to 20 mg. (0.16 to 0.32 grain) weekly in conjunction with thyroid extract. In some cases there is marked secondary anemia. This should be treated in the usual manner.

CRETINISM

It has been shown that the occurrence of cretinism can be greatly decreased by the administration of iodine to the pregnant woman and to children as described above under simple goiter. The great importance of this prophylactic treatment lies in the fact that changes in the nervous system occur during fetal life that are in part irremedial. Furthermore the abnormality in the infant is often unnoticed until the age of twelve to eighteen months. By this time the prenatal changes have progressed so far that the mental development of the child may never reach normal.

The treatment of the cretin is similar to that of the myxedematous patient. The initial dose of thyroid extract depends on the general condition of the child, the pulse rate, and weight. Desiccated thyroid extract 1 to 4 grains may be given in one or two two doses daily. In children the effect of thyroid medication is

evident sooner than in adults. Usually in four to five days the temperature and pulse rate increases, the weight decreases, the child becomes more alert. Diarrhea may occur. The optimum dosage must be determined as in the case of myxedema. The optimum dose does not mean the maximum dose a patient can bear, but the smallest dose compatible with the maximum improvement and sense of well-being. If anemia is present this should be treated.

GRAVES' DISEASE

I have not chosen the term "exophthalmic goiter" for this disease because it suggests that the condition is primarily due to pathologic changes in the thyroid gland, whereas the relationship between it and the thyroid gland has not been proved. It still remains a question whether it is a general constitutional disease in which the thyroid gland becomes involved or a disease of the thyroid gland that causes constitutional symptoms. The more I study the disease, the more I am impressed by the type of person who is susceptible to this disease, namely, young adults, especially women, between the ages of twenty to thirty years, who belong to that group described under various terms, such as autonomic imbalance, unstable vasomotor nervous system, etc. In such individuals infectious diseases, especially influenza, pneumonia, diphtheria, acute rheumatic fever, typhoid fever, and incipient tuberculosis; focal infections, such as apical abscesses, tonsillitis and sinusitis; pelvic disease, such as fibroids, malposition of the uterus and chronic pelvic infection, seem to play an important rôle as precipitating causes of Graves' disease.

The acute cases develop in a few days or weeks following virulent infections, the puerperium, etc. The first symptom to develop is usually tachycardia; it may be the only one for weeks and be looked upon as a true cardiac disorder until one realizes that it is not affected by digitalis or the termination of the infection or other precipitating cause. In several instances I have known it to start on the occasion of a puncture of the sinus where novocaine with adrenalin was used as a local anesthetic. Tremor and weakness follow closely upon the tachycardia and later the characteristic stare and exophthalmos may be evident,

but the change may be so slight that it is unobserved; marked pigmentation of the eyelids occurs in some cases. The enlargement of the thyroid gland is usually the last sign to develop; the gland may be only slightly full and soft or it may be very large, uniform, and soft. The basal metabolic rate is always high. Since the prognosis is excellent in the cases treated early, I lay especial stress on the importance of an early diagnosis and emphasize the fact that many cases are not recognized until late in the disease because the goiter and exophthalmos may be very inconspicuous.

The treatment of acute Graves' disease is the same as that described for the chronic form except that surgery is to be avoided in the early cases, especially in those with only a moderately enlarged gland. I have had excellent results with bed rest alone. In those in whom time was so important a factor that a sufficiently long period of rest was impossible, I have used *x*-ray treatment after a rest in bed of three to four weeks. The following case history is typical of acute Graves' disease.

The patient is a man of thirty-seven years whose history and physical condition had been accurately followed for many years and a diagnosis made of hypothyroidism based on a tendency to obesity, slow pulse, low blood pressure and low metabolic rate, etc. For several months he had not been feeling very well, he had less energy and fatigued more easily than usual, he was conscious of a tremor in the muscles of the legs and arms. He then contracted a cold complicated by a sinusitis for which the antrum was punctured under local anesthesia of novocaine and adrenalin. While in the doctor's office he developed a marked tachycardia, a feeling of faintness and weakness. He was put to bed immediately but the tachycardia continued. When I first saw him, tachycardia and a rise in systolic blood pressure of 20 points over his normal were the only definite findings. After a rest in bed of four days the basal metabolic rate was plus 37 per cent. An electrocardiogram showed a simple tachycardia. After one week there was a definite widening of the palpebral fissure, a characteristic stare, slight exophthalmos and pigmentation of the skin of the eyelids. Tremor of the hands was never marked but a fine movement could be felt in the muscles of the arms and legs. After two weeks the thyroid was definitely but slightly fuller than it had been, and very soft.

The patient was kept quietly in bed on luminal (gr. $\frac{1}{2}$) three times a day and syrup of hydriodic acid, min. 15, once a day. After one week he showed definite improvement in the pulse rate, and the tremor and the subjective sense of inward trembling disappeared.

At the end of six weeks the patient had no symptoms. The exophthalmos and stare were much less noticeable, the tremor had disappeared, the pulse was normal when quiet, but it increased 20 to 30 points on slight exertion. The systolic blood pressure remained higher than his normal. The basal metabolic rate was plus 1 per cent. After ten weeks he showed no abnormal symptom or sign except the elevated blood pressure. He was first allowed to sit up for fifteen minutes the first day and the activity gradually increased. The change in the pulse rate was out of proportion to the exertion for four weeks but it slowly decreased until it fell to 80 with the normal reaction to exercise at the end of the twelfth week. (His usual pulse previous to this illness had been 60.) He returned to work as an executive in a large business after the third month and has remained well for eight months. He still continues to rest one hour at noon and to stay in bed on Sundays. He has continued to take 1 mg. of iodine once a day.

Chronic Graves' disease is the characteristic picture known as exophthalmic goiter, Basedow's disease, etc. David Marine classifies the disease as (1) the primary or classical and (2) secondary or atypical groups. The former needs no explanation. In the second group he includes all those cases variously described as hyperthyroidism, thyrotoxicosis, toxic adenoma, etc. in which all the typical signs and symptoms of Graves' disease have not developed. I have chosen Marine's classification because it emphasizes that all these conditions are but various stages in the development of the same disease.

Every case of Graves' disease is primarily a medical problem. The treatment is based on the supposition that it is of unknown etiology, that the pathologic physiology of the disease involves, (1) the sympathetic nervous system; (2) the cardiovascular system, and (3) the thyroid gland and that the basal metabolic rate is definitely elevated. The underlying principle of the treatment is physiologic rest. The exact methods to be used cannot be definitely stated because the financial condition of the patient influences so largely the feasibility of any procedure. It is therefore necessary in taking the history to investigate carefully the social economic status of the patient. Before formulating any plan it is well to determine (1) the length of time the patient can be away from work; (2) the patient's present and final disability for his present occupation; (3) the possibility of an operation, either immediate or later; (4) the pa-

tient's attitude toward an operation. With these facts in mind a course of treatment may be planned.

As I have stated above, the fundamental principle of treatment is rest. To secure proper rest the patient must be confined to bed for a prolonged period of six to eight weeks in surroundings conducive to both physical and mental quiet and free from all disturbing associations. The very nature of the disease demands the use of sedatives in doses sufficient to produce complete mental and physical rest and a hypnotic if necessary to secure a long night's sleep. Luminal $\frac{1}{2}$ grain three or four times a day and bromides 20 to 40 grains at bedtime give good results.

Iodine should also be given. The size of the dosage depends upon how long a period of rest the patient can afford and whether an operation is contemplated. The ideal to be strived for is to return the patient to normal without operation if possible. In this case the dosage of iodine is 10 mg. daily. Close observations should be made of the patient's weight, pulse rate, and temperature and the basal metabolic rate determined at weekly intervals. In most cases the condition of the patient shows decided improvement and the basal metabolic rate decreases in ten to fourteen days. If there is no contraindication this routine is continued until the pulse and basal metabolic rate approach normal. Usually this requires three to four weeks. This dosage of iodine is then decreased 1 mg. daily until it is reduced to 1 mg. and then the dosage is experimented with until the optimum dose is determined as judged by the patient's pulse, weight, and basal metabolic rate. After these factors are normal for about two weeks the patient is allowed to sit up, starting with fifteen minutes once a day, then fifteen to thirty minutes a day continuing to increase the activity allowed according to the reaction of the patient in terms of pulse rate and fatigue. When the patient is able to remain up all day, a rest period before and after each meal must be insisted upon for many months.

The dosage of iodine should be reduced to 1 to 2 mg. once a day after the first eight to ten weeks. This dose is continued for an indefinite period, but under regular observation.

The diet in these cases must afford sufficient calories to meet

the metabolic needs, and be balanced in carbohydrates, fats, proteins, and vitamins. Alcohol, coffee, tea, and cigarettes should be eliminated.

If there has been a diarrhea, colon irrigations are beneficial.

If the economic position of the patient prohibits such a long period of rest as herein prescribed, an operation should be advised at the outset. It should be preceded by at least two weeks' rest in bed under iodine medication.

If the condition of the patient becomes worse under the above treatment, or if the condition is not distinctly better at the end of a month, then an operation on the thyroid gland should be advised. When an operation has been decided upon the dosage of iodine should be about 100 mg. three times a day (Lugol's solution 10 to 15 minims) for ten to fourteen days depending upon the pulse and basal metabolic rates. Postoperative this dose of iodine is continued for a week and then decreased gradually until it is reduced at the end of seven to ten days to 1 mg. The patient is then given this dose daily for an indefinite period. The postoperative medications are best given rectally in starch paste because of the discomfort of swallowing. The iodine may be given in one dose.

The postoperative care of these patients is extremely important. They should be kept in bed for from three to four weeks and then allowed to get up for increasingly longer periods daily according to their reaction in terms of pulse rate, fatigue, and basal metabolic rate. They should begin exercising gradually and should increase it according to their reaction to it as does a cardiac patient. It requires usually six months before the patient should attempt to return to work.

After these patients are discharged they should have an environment free from strain and worry, in which they can rest two to three hours in mid-day and ten to twelve hours at night. They should be seen by the doctor every three or four weeks and the weight, pulse rate, basal metabolic rate, and general condition followed. If they develop a myxedema they must be given thyroid extract sufficient to maintain a normal basal metabolic rate.

The treatment of cardiac decompensation in diseases of the thyroid does not differ from that in any other disease. Digitalis will decrease the pulse rate only insofar as the tachycardia is due to decompensation. It will often control the auricular fibrillation of thyrotoxicosis. If it does not quinidine sulphate should be tried unless the fibrillation is chronic. The initial dose is 0.2 Gm. (grain 3) and is repeated in two hours. If there is no contraindication this dose is given every four hours for a week or ten days. It is then discontinued if the fibrillation has not ceased. Tachycardia is the most persistent symptom in many of these patients. It is often unchanged by any medication, by surgery, or *x*-ray. It is often controlled by iodine medication, the dosage of which must be determined by experimentation with each individual patient.

The results of roentgen ray therapy are variable and I know of no way to foretell its value. It is most effective in those cases with slight increase in the size of the thyroid gland. I use it where medical treatment alone is ineffective and surgery is refused or is not advisable.

A differential diagnosis must be made between Graves' disease and neurocirculatory asthenia, simple tachycardias of unknown etiology, and incipient tuberculosis. It is extremely important to remember the frequent association of Graves' disease and incipient tuberculosis and to plan any régime to include treatment for both diseases where they coexist.

Adenomas never develop in a normal thyroid gland, but only in a gland that has been the seat of either a simple goiter or of Graves' disease. I have classified them therefore as complications of these two diseases. In either case adenomas usually cause no symptoms until about the menopause or during pregnancy when they may develop into an atypical Graves' disease. By the use of large doses of iodine in an attempt to reduce the size of the adenoma, a thyrotoxicosis may be precipitated at any age.

The only satisfactory treatment for an adenoma is the surgical removal of the mass. The results are excellent if the operation is performed before the thyrotoxicosis affects pathologic

changes in the heart muscle or sympathetic nervous system or the rest of the thyroid tissue. The important question then is when to advise operation in a patient with an adenoma, but without any symptoms. Since these patients are prone to develop symptoms during pregnancy and at or near the menopause, it seems wise to remove the adenoma before these occur. The possibility of a carcinoma developing in an adenoma is another argument in favor of an operation.

Iodine should not be given to patients with adenomas except in small doses of not more than 1 mg. once a day and then under close observation. In large doses it may initiate a thyrotoxicosis especially in patients near the menopause.

Roentgen ray therapy is of very little value in the treatment of an adenoma of the thyroid gland. I use it only in cases that are markedly toxic where surgery is impossible and I find that it occasionally gives satisfactory results.

The deleterious effects of iodine medication in Graves' disease are well illustrated in the following case history.

An unmarried woman thirty-one years of age was seen by a doctor who made the correct diagnosis of Graves' disease and prescribed Lugol's solution MX three times daily. In ten days her pulse was reduced from 104 to 84 and she had gained 2 pounds in weight and felt much better. The dose of the Lugol's solution was reduced to MV three times a day. Three weeks later she did not feel as well as before—she had a more rapid pulse, had lost weight and was very nervous and had a more marked tremor. The dose of Lugol's solution was then increased again to MX three times a day. One week later the pulse was very rapid, the thyroid gland was larger, the exophthalmos increased and the loss of weight marked. Her condition was considered so serious that an operation was advised.

This patient demonstrates the course of events that usually occurs when large doses of iodine are given in Graves' disease. At the end of the first ten days there is a marked improvement in the pulse rate, weight, basal metabolic rate, etc. If the iodine is continued the reverse changes occur—the pulse rate begins to increase, the basal metabolic rate rises, the weight decreases, the thyroid gland enlarges and all the signs of toxicity increase so that an operation is necessary.

If the large doses of iodine are suddenly discontinued after

ten to fourteen days an acute exacerbation of symptoms may occur and continue for two to three weeks, and then gradually subside to the original condition. Therefore if the iodine medication is to be discontinued without operation the dosage should be decreased gradually by 10 mg. daily.

Malignant growths in the thyroid are not common, but it is very important to remember that they may occur. Carcinoma is the more usual form; sarcomata are rare. It is impossible to make an early diagnosis of a neoplasm, but it should be suspected when the size of an adenoma increases steadily and the consistency is very firm, and neither the size nor the consistency fluctuates as is the case in simple adenoma. A diagnosis is even more difficult in the carcinomas that develop in the parenchyma.

Carcinomas of the thyroid metastasize typically to the bones of the skull, the sternum, vertebrae, ribs, pelvis, clavicle, etc. The lungs are also frequently involved and more rarely other viscera. The growth is usually slow.

The treatment of neoplasms of the thyroid is surgical in the early cases and roentgen ray or radium therapy in cases where a positive diagnosis can be made.

Thyroiditis is an acute inflammation of the normal thyroid gland. It occurs as a complication of an acute infection especially in influenza, pneumonia, and typhoid fever. The first symptom is usually pain in the thyroid gland with local swelling and difficulty in swallowing. There may be chills, fever, nausea, and vomiting. Tachycardia usually develops early and may be persistent for weeks after the disappearance of the local signs. In 2 cases which I have seen recectly the basal metabolic rate has been elevated for several weeks after the temperature has become normal. It then became normal and has remained so. An abscess may form in the gland and require surgical treatment.

These cases require rest in bed under sedatives and local applications of cold. Aspirin will often relieve the local pain. I find 10 mg. of iodine once a day for several weeks is beneficial.

The following case illustrates the course and treatment of the disease:

A woman forty years of age, a lady's maid, had an upper respiratory infection diagnosed as "grippe." She had a rhinitis, sore throat, and a temperature and generalized aching but she did not go to bed. Following this she did not regain her usual vigor but felt constantly fatigued, became conscious of her heart; then she felt pain and swelling in her thyroid, the pain radiated to the region of the second and third cervical nerves. When I saw her the thyroid gland was swollen and tender, the pulse was 120, the temperature was 101 F. She was put to bed and given 10 minims of syrup of hydriodic acid daily, ice packs on her neck, and luminal ($\frac{1}{4}$ grain three times a day and $\frac{1}{2}$ grain at bedtime). She ran a temperature for ten days fluctuating between 100 and 101 F. which went to normal by lysis. The swelling of the gland gradually subsided over six weeks. A basal metabolism test done a week after the temperature became normal was +25 per cent. After four weeks it became normal and it has remained so. The pulse rate gradually became normal. She has now been well with a normal pulse and basal metabolic rate for four years.

CLINIC OF DRS. GEORGE BAEHR AND
PAUL KLEMPERER

MOUNT SINAI HOSPITAL

THROMBOSIS OF THE PORTAL AND OF THE HEPATIC VEINS[1]

DOCTOR BAEHR: Any constitutional disease which predisposes the individual to venous thromboses may result in thrombotic closure of either the hepatic or the portal veins. They may suddenly become occluded aseptically as a complication of a variety of diseases such as syphilis, polycythemia vera, migrating phlebitis. Any adjacent inflammatory or neoplastic process may compress them or damage their wall and in this manner initiate the thrombus. Conditions which produce unusual venous stasis, especially cirrhosis of the liver, may become complicated by a thrombosis of the portal vein. And finally isolated changes in the wall such as atherosclerosis of the portal vein or its branches or local endophlebitis of the hepatic veins may be responsible for the closure.

Probably because the hepatic veins enter the inferior vena cava at an awkward angle, and may at times sustain the dragging influence of a ptosed liver, they are quite susceptible to chronic mural changes. And yet in spite of influences which may precipitate the formation of an aseptic thrombus in either the hepatic veins or in the portal, both conditions are rare.

It is not generally realized that constitutional disturbances such as polycythemia vera with its accompanying thrombocytosis (increase in blood platelets) or the thrombocytic form of so-called "Banti's disease" may result in a thrombosis of the

[1] From the Proceedings of the Weekly Clinical-Pathological Conferences of the Mount Sinai Hospital, New York.

hepatic or the portal veins. Nor is it generally appreciated that they may become involved as part of that very common but obscure disease, migrating phlebitis. The 2 cases which we are now to present are, therefore, of more than ordinary interest.

The diagnosis of portal vein thrombosis is difficult because its most conspicuous symptom, ascites without general edema, is more commonly the result of an uncomplicated cirrhosis of the liver or of a peritoneal or retroperitoneal neoplasm. If the splenic vein is also occluded, the resulting splenomegaly may make one think of Banti's disease. If distal tributaries of the portal, the branches of the superior mesenteric become closed, the sudden occurrence of symptoms of intestinal hyperperistalsis, frequent bowel movements with or without bloody stools, or the sudden onset of ileus in a patient who has had an obscure ascites might give a clue to the correct diagnosis.

The symptoms of hepatic vein thrombosis are much more characteristic than those of portal vein closure and an accurate diagnosis is, therefore, more frequently possible. Pain in the right upper quadrant of the abdomen which radiates to the back and to the right or left shoulder blade, a huge tender liver, the simultaneous appearance of an enlargement of the spleen, and of ascites paint a distinctive clinical picture.

HEPATIC VEIN THROMBOSIS

In the first patient whom we now present, the diagnosis was accurately made by Dr. B. S. Oppenheimer immediately after the patient's admission as endophlebitis and thrombosis of the hepatic veins. I tell you this so that you can follow the clinical story in detail and again pick out the clinical facts which justified the diagnosis.

The patient was a woman, forty-nine years of age, who was first admitted to the hospital fourteen years ago, in January, 1916. The story at that time was that for five years, since 1911, she had suffered frequent attacks of cramp-like pain in the epigastrium which radiated to the back and left shoulder, occasionally to the right shoulder. The attacks of epigastric pain were sometimes associated with fever and vomiting. They recurred very frequently, usually every few weeks. On one occasion she thought that she was slightly jaundiced after an attack.

When the patient first came under our observation in 1916 the liver was found to be enlarged; the lower border could be felt about two fingerbreadths below the free border of the ribs and seemed smooth but definitely tender. Wassermann reaction was negative.

Because the diagnosis was obscure, an exploratory laparotomy was performed and an ulcer was found on the anterior wall of the first portion of the duodenum just outside the pylorus. It was excised with a cautery and then the opening infolded. A partial pyloric exclusion resulted from this procedure, and then a posterior gastro-enterostomy was made. The patient remained well thereafter for several years and gained 62 pounds in weight.

In 1922 severe cramplike pains in the epigastrium recurred, which would sometimes radiate to the back and the right shoulder. They would usually begin immediately after meals and would disappear a few hours later when the patient was again hungry. Her appetite remained good but she was afraid to eat and for this reason lost 42 pounds in weight during the next seven years. During this long period the attacks continued at irregular but frequent intervals.

Finally, three weeks ago, after a very severe attack, she became jaundiced. The jaundice persisted for three weeks but the stools never became clay colored. During this unusually severe attack of pain, she vomited frequently. After the pain subsided, not only was jaundice noticed but the patient herself discovered several masses in her upper abdomen which grew rapidly in size. The severity of the pain three weeks ago, the occurrence of jaundice and the appearance of abdominal masses were sufficiently alarming to induce her to enter the hospital.

At this time she still appeared to be well nourished in spite of having lost 42 pounds. The skin and conjunctivae had a subicteric tint. The skin of the body was loose and inelastic, indicating the great loss in weight. The lower edge of the liver could now be felt three and a half fingerbreadths below the free border of the ribs. It was smooth and definitely tender. In the left upper quadrant a mass, apparently the spleen, could be felt, the edge of which extended three fingerbreadths below the costal margin. It also seemed to be tender.

Her hemoglobin at this time was 110 per cent and the red blood count about 6,000,000. The leukocyte count was 9950, of which the polynuclear leukocytes constituted 65 per cent. The blood pressure was 105 systolic, 86 diastolic. The urea nitrogen was normal, 13 mg. per 100 cc.; the cholesterol was also normal, 148 mg. per 100 cc.

A roentgen examination of the gallbladder revealed the presence of transparent calculi. This finding seemed to account satisfactorily for the numerous attacks of right upper quadrant pain, which were sufficiently typical in character and radiation to justify the diagnosis of cholelithiasis. But the hepatosplenomegaly puzzled the surgeons and an opinion was therefore asked of the medical consultant, Dr. B. S. Oppenheimer. He summed up the clinical findings as including polycythemia, marked jugular vein pulsation, large firm tender liver, a tender gallbladder, splenomegaly and low-grade fever. He therefore suggested that the most likely diagnosis which would explain all the findings was an hepatic vein thrombosis, although there also

seemed to be a possibility that the enlargement of the liver and spleen might be due to a long standing chronic infection of the biliary passages. Exploratory operation was advised because he thought that the tender, palpable gallbladder and the definite *x*-ray findings of cholelithiasis alone justified a laparotomy.

At operation two liters of clear, yellow fluid were encountered in the peritoneal cavity. After this was evacuated, the liver was found to be greatly enlarged and intensely congested. It was stony hard, but was smooth. There were dense adhesions of the omentum to the peritoneum and greatly dilated vessels could be seen in the omentum coursing toward the liver. The gallbladder was found to be thickened and there were many small pigmented stones found in the gallbladder and the cystic duct. A cholecystotomy was done and the gallbladder drained.

As noted by one of the surgeons the appearance of the liver seemed to confirm the diagnosis of thrombosis of the hepatic veins, for in the absence of heart disease no other condition could produce such an enormous congestion of the organ, as well as splenomegaly and ascites.

After the operation the patient slowly sank into collapse. Her blood pressure dropped steadily until finally the systolic was only 80. At first ascitic fluid drained profusely from the wound. From the tube which drained the gallbladder there was only a slight biliary discharge. Finally the serous discharge from the wound ceased, ascites increased rapidly and now marked edema of the legs was evident. The pulse became increasingly rapid and thready until the patient died three weeks after the operation.

Dr. Klemperer: Figure 77 shows the dome of the liver and you can recognize the vena cava inferior and two hepatic veins. In a normal specimen one can recognize the opening of the hepatic veins as a wide ostium, and we are easily able to introduce a forceps into each branch; in this liver it is quite impossible, and the hepatic veins at their entry into the vena cava do not even admit a probe. This is due to the fact that the lumina of the two main hepatic veins are funnel shaped, narrowing down very abruptly and soon become completely obliterated. Figure 78 shows the obliteration of the hepatic veins by an old recanalized thrombus. There is no neoplastic or inflammatory process in the vicinity of the veins which might be responsible for the original thrombosis.

The cut surface of the liver presents a picture of extreme passive congestion. We find on the section fresh thromboses of numerous intrahepatic branches of the hepatic veins. These, of course, are more recent secondary thrombi caused by the re-

tardation of the blood stream which has followed the obliteration of the main branches.

The spleen is considerably enlarged. It weighed about 500 Gm. We find the lumen of the splenic vein also completely obliterated by an old organized thrombus which is perforated by numerous canaliculi. The abdominal cavity contained a very large amount of infected, ascitic fluid which was the immediate cause of death. A subacute cholecystitis was also present.

In addition to an old gastro-enterostomy opening, the stomach showed a diffuse congestion with several superficial ulcera-

Fig. 77.—Shows the dome of the liver with two funnel-shaped ostia (VH) opening into the inferior vena cava.

tions. These must be considered ulcerations of the mucosa due to the circulatory disturbance. Very many collateral veins are to be found connecting the vena cava inferior system with the portal system, the varicose veins of the esophagus being an example.

Since the first description of this picture of obliterating endophlebitis of the hepatic veins by Chiari years ago, there have been many cases reported. The cause is usually difficult to ascertain. In a few cases fortunate observers have found a tumor or an in-

flammatory lesion in the immediate vicinity. A gumma at the junction of the hepatic veins and inferior vena cava has been responsible for the thrombosis in several instances. Other observers have found chronic inflammatory changes in the wall of the vein. In our case we are unable to find any gross lesion at this site, or even any microscopical evidence of damage in the venous wall. In fact the wall of the hepatic vein is perfectly normal (Fig. 78). Yet the lumen of the hepatic vein is obliter-

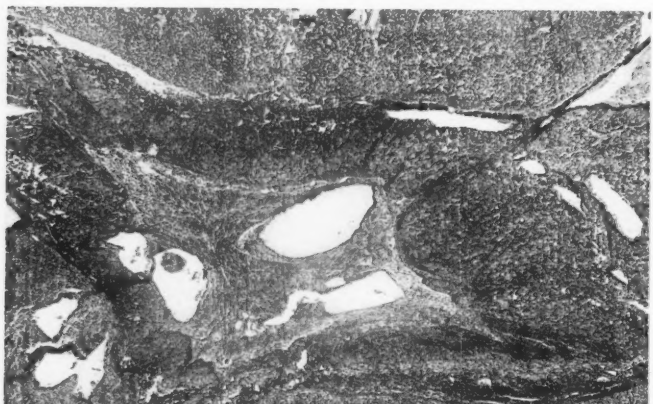

Fig. 78.—Low power showing the obliteration of the hepatic veins by a recanalized thrombus.

ated by an organized thrombus which has been recanalized by four blood vessels. The elastica interna is perfectly normal. The muscular wall shows no evidence of disease.

The splenic vein also shows a completely obliterated lumen, so extensively recanalized as to reproduce a picture which one might compare with a cavernoma. Again the elastic interna and the muscular wall are perfectly normal. The portal vein is

patent and in one place shows a plaque on the wall which proves on microscopical study to be an organized mural thrombus.

The absence of any lesion in the wall of the obliterated hepatic and splenic veins or even in their immediate proximity obliges us to consider some constitutional cause as an etiologic factor.

DR. BAEHR: Any disease of the liver, due either to an acute or chronic infection, to syphilis or to neoplasm, can produce thrombosis of the hepatic veins. But no condition of this nature was present in our case. Individuals suffering with polycythemia vera frequently show a tendency to thromboses in veins, capillaries, or arteries. Even the capillary bed in a local area of the skin may become closed. The tip of the nose, for example, is a frequent site, and the characteristic skin lesions of polycythemia are very well known to the dermatologists. Thrombosis of arteries or of veins is even more common. In a recent case which I observed, a slowly progressive intracerebral thrombosis gave rise to symptoms which suggested an intracranial neoplasm. In another case observed last year, the thrombosis occurred in an artery of the leg.

The occurrence of spontaneous thromboses anywhere in the body should always impel one to look for an underlying constitutional cause such as polycythemia. In this disease there usually exists not only an erythrocytosis but also a thrombocytosis, an increase in blood platelets. In our case the primary thrombosis of the hepatic and the splenic veins may very possibly have been the result of polycythemia.

A primary nonsuppurative thrombosis of the hepatic veins may also follow a migrating phlebitis of the leg. I have seen the process spread from the leg to the abdominal wall and finally to the hepatic veins, resulting in a clinical picture as characteristic as the one which we have just presented.

PORTAL VEIN THROMBOSIS

In the next case a somewhat similar clinical picture was observed, but with some distinctive differences.

This man, forty-five years of age, began to prepare for his present illness with a chancre in 1899, thirty years ago, when he was fifteen years of age.

He remained well until three years ago when he began to suffer from pain in his feet, especially on walking. The feet were red and cold. After several months the fourth toe on the right foot became gangrenous. He was admitted to our thrombo-angiitis obliterans clinic where a diagnosis of Buerger's disease was made and he was given intravenous injections of hypertonic saline solution and other appropriate treatment. At this time both the right dorsalis pedis and the posterior tibial arteries were obliterated and the oscillometer reading on the right leg was zero. In the course of the next year gangrene was arrested, the pain and redness of the feet disappeared and the patient became quite well and active again. Oscillometer readings now showed a fair return of the circulation in the right foot, and some pulsation in the dorsalis pedis vessel was detected by palpation.

A year ago the symptoms recurred and this time a small area of gangrene appeared on the third toe on the left foot. He was again treated intravenously for a period of three months and again became so well that he discontinued treatment. The right dorsalis pedis artery now had a good pulsation, evidence of recanalization. The right posterior tibial was still closed. Oscillometric readings on the right leg now equalled the left. None of the vessels on the left foot were ever closed.

Three weeks ago he noticed increasing size of his abdomen. The only subjective symptoms were a feeling of heaviness in the abdomen, which came on usually after meals. The abdomen increased steadily in size. It also seemed to him that the skin of his face and body was darker in color. There was no abdominal pain and the only other subjective symptoms were that he passed urine more frequently, had some urgency in urination and became increasingly constipated. After his abdomen had been quite swollen for ten days he first noticed slight swelling of the ankles.

Upon admission to the hospital he appeared to be markedly emaciated. There were patches of deepening pigmentation of the skin of his face and body. There was no icterus. Characteristic Argyll-Robertson pupils were present. There were signs of old, healed tuberculosis at both apices.

The abdominal wall was exceedingly thin. The superficial abdominal veins stood out prominently and gave one the impression that there must be some obstruction to the venous flow within the abdomen. The great distention of the abdomen was due to an immense ascites.

Both dorsalis pedis vessels could be felt pulsating, but the right posterior tibial artery was closed. There was no edema of the legs at the time of admission.

The diagnostic possibilities were considered to be cirrhosis of the liver, possibly luetic, and a malignant neoplasm of the peritoneum. The pupillary changes and positive Wassermann seemed to speak in favor of a luetic cirrhosis. The emaciation rather inclined some to consider the condition a neoplasm involving the peritoneum. One clinician suggested the possibility of hepatic vein thrombosis, the sequel of thrombo-angiitis obliterans.

x-Ray of the abdomen after inducing a pneumoperitoneum revealed a large liver and a large mass in the left upper quadrant of the abdomen, neither of which could be palpated because of the ascites. The hemoglobin was 92 per cent; at another time 96 per cent, with about 5,500,000 red cells. The

leukocyte count was 17,200, 88 per cent polynuclears. Blood pressure was 122 systolic, 80 diastolic. Liver function test revealed a 20 per cent retention of bromsulphonephthalein thirty minutes after injection which indicated a very slight, not very important liver damage. The icteric index was only ten. Both observations eliminated the diagnosis of hepatic vein thrombosis as well as the possibility of diffuse cirrhosis of the liver.

Abdominal paracentesis was done repeatedly, three to five liters being removed at various times. The fluid was clear, straw colored, and had a low specific gravity, 1.005. It was therefore a transudate.

After a week in the hospital the patient suddenly began to have persistent diarrhea and to vomit. His general condition then failed rapidly, the pulse becoming rapid and poor. Blood chemical analysis now showed a urea nitrogen of 50 mg. per 100 cc. Vomiting and diarrhea continued, he developed hiccough and finally died ten days after admission. At the time of death, the diagnosis was still uncertain, most of the clinicians being inclined to regard the condition as a neoplasm involving the peritoneum and producing ascites. No special thought seems to have been expended upon the significance of the final episode, the sudden onset of diarrhea and vomiting which finally ended in death.

DR. KLEMPERER: When we opened the abdomen and had evacuated an extensive ascites we noticed that the small intestines were of a dark red color. This immediately suggested a thrombosis of the superior mesenteric vein. And we found the lumen of this vessel obliterated by a rather fresh thrombus. The wall of the vein was markedly thickened. We also found that the smaller branches of the mesenteric veins were obliterated by fresh thrombi.

Conspicuously dilated veins were then encountered in the gastrosplenic ligament, on the abdominal surface of the diaphragm, in the lesser omentum and in the falciform ligament of the liver. The umbilical vein in the round ligament was patent. The esophagus, the left suprarenal, the hemorrhoidal and prostatic veins also showed conspicuous dilatation. These were all evidences of an attempt to provide collateral venous circulation for an obstruction in the portal.

Following the course of the mesenteric vein upward, we first observe that the lesser omentum, which in anatomical text-books is described as the ligamentum hepatoduodenal is very markedly thickened. Cross section of this ligament, in which the important vessels and the bile ducts run to the liver, reveals that the lumen

of the portal vein is closed by a thrombus. The wall of the portal vein appears very markedly thickened (Fig. 79).

In another section you can recognize that the entire lesser omentum around the portal vein is perforated by numerous small blood vessels. We even see a conspicuous dilatation of the cystic vein. There are new channels formed to carry blood to the liver to compensate for the closure of the portal. In chronic portal thrombosis not only are the hepatofugal collaterals, *i. e.*,

Fig. 79.—Coronal section through the hepatoduodenal ligament showing the cavernoma-like formation and the thrombosed portal vein within the thickened ligament.

the anastomoses between portal and inferior cava developed, but also hepatopetal collaterals, *i. e.*, between portal or mesenteric and the liver are formed because the impediment in the portal circulation is entirely extrahepatic. In atrophic cirrhosis of the liver the obstruction is intrahepatic, and therefore only the hepatofugal collaterals become enlarged.

On further frontal section which is carried through the liver hilus we find that the collateral veins are so numerous as to pre-

sent the appearance of cavernomatous tissue. The connective tissue at the hilus looks like a sponge. Even within the liver the same characteristic cavernomatous tissue is seen to follow the ramification of the Glisson capsule (Fig. 80).

We are dealing, therefore, with an old thrombosis of the portal vein and a resultant cavernomatous transformation of the lesser omentum, the hepatoduodenal ligament. The literature on this condition may be found in an article which I recently wrote.[1] Since its publication, I have found five other case reports by O. Ehrentheil from the Institute of C. Sternberg: W. M. W. 75, 1848, 1925 and an article by S. Van Crefeld and W. A. Levy:

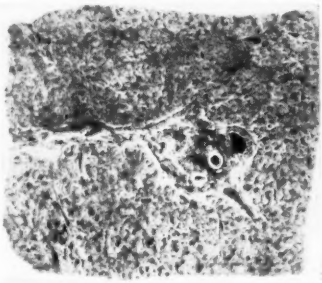

Fig. 80.—Showing the cavernoma-like formation surrounding a large intrahepatic branch of the portal vein.

Nederl. Tijdschr. Voor Geneesk, 72, 1929, 3649. The term "cavernomatous transformation" of the portal vein, which was first used for this condition, is incorrect. It is not a cavernoma. The extensive recanalization of the obliterating thrombus plays a part in its formation but the venous vascularization of the tissue around the portal vein is even more conspicuous. These new channels play a more important rôle in the formation of the cavernomatous tissue than the newly formed vessels within the thrombosed portal vein.

In every one of the reported cases the spleen was described as being very large, and you also see here a very large spleen.

[1] Paul Klemperer: Cavernomatous Transformation of the Portal Vein, Its Relation to Banti's Disease, Archives of Pathology, 1928, vol. 6, p. 353.

It weighs 1200 Gm. and shows large infarcts, old and recent. These were caused by emboli originating in mural thrombi on the aorta. The splenic vein is completely obliterated and appears as a fibrous cord.

In addition to his abdominal condition, there was an obliterating thrombosis of the right coronary artery with recanalization; a diffuse myocardial fibrosis was therefore found. Unfortunately, we were not able to examine the arteries of the extremities to make sure of the nature of his peripheral arterial disease.

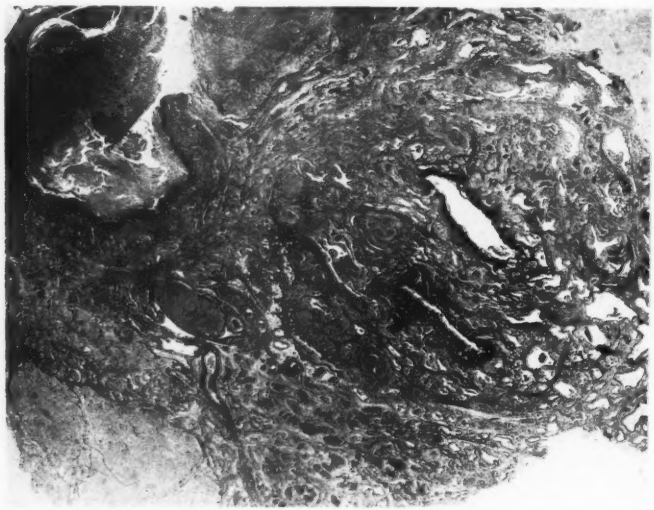

Fig. 81.—Low power showing the thrombosed portal vein in the left upper corner and the cavernoma-like transformation of the hepatoduodenal ligament in the right lower corner.

If we now turn to the histologic slides, I present first a low power picture of a cross section through the hepatoduodenal ligament (Fig. 81). You recognize at the periphery the thrombosed and completely obliterated portal vein. The recanalization of the thrombus is not as conspicuous as the numerous new vascular channels in the adjacent part of the much thickened ligament, which are responsible for the picture of a cavernoma.

From this picture you can recognize that the contention of those authors who considered the condition a primary malformation or a vascular neoplasm of the portal vein is wrong.

At a higher magnification (Fig. 82) the same cavernomatous tissue is visible inside the liver, within the portal vein as well as in the periportal tissue. I should like to call your attention to the marked hypertrophy of the media of the hepatic artery, an

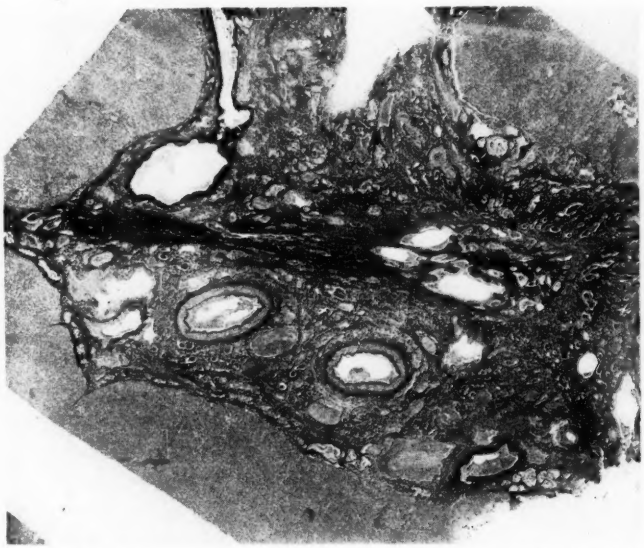

Fig. 82.—Low power showing the obliteration and recanalization of the intrahepatic portal branch with the surrounding extensively vascularized Glisson capsule. Note the hypertrophied media of the hepatic artery.

observation you can make in every instance in which the circulation in the portal vein is embarrassed. Apparently in an attempt at compensation, the hepatic artery becomes hypertrophic.

The histologic examination is exceedingly important in order to gain an accurate understanding of the pathogenesis of portal thrombosis. Sections taken from various levels reveal the following pictures: The lumen in Fig. 83 is seen to be filled with

Fig. 83.—Section of the portal vein showing the organized thrombus, the markedly thickened intima and media. Note the interruption of the adventitial muscle coat by scar tissue. (Left side of the picture.)

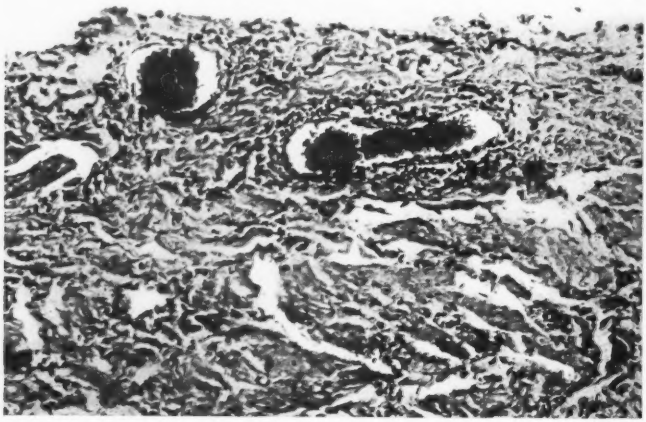

Fig. 84.—Higher power of same section as Fig. 83 showing perivascular infiltration of the adventitia.

a recent thrombus, the periphery of which has already undergone complete organization so as to blend with the markedly thickened intima. The new cellular connective tissue is interspersed with large mononuclear cells and lymphocytes. Upon closer inspection one recognizes that the connective tissue is not alone composed of coarse and fine collagin fibrils, but even smooth muscle cells are encountered, and in a few places a network of delicate elastic fibers is found. Where the thrombus is retracted from the wall of the vein, a lining of flat endothelial cells is recognized.

Fig. 85.—Section of the wall and surrounding fat tissue of a mesenteric vein showing marked cellular infiltration.

The thickening of the intima varies in different sections. In places its width is equal to that of the rest of the venous wall, and here it is formed of dense connective tissue containing few blood channels and very little evidences of blood pigment. The internal elastic lamina is recognized as a distinct single band, showing no tendency to splitting into fibrils, although it is often interrupted for longer or shorter distances by transverse breaks.

The circular musculature of the media is often of uneven width and in the different sections shows marked variations in the amount of elastic fibers. But the most important and conspicuous alteration is the fact that the musculature of the media is much thicker than normally. Here and there it is interrupted by dense connective tissue scars containing coarse elastic fibrils. Especially in the outer zone it is sparsely infiltrated with lymphocytes and a few polynuclear leukocytes. The adventitia, with its broad mantle of longitudinal muscle bundles, is infiltrated with round cells having a conspicuous perivascular arrangement. In some places the muscle bundles are interrupted and replaced by connective tissue.

Sections from the splenic vein show the lumen obliterated by a plug of dense connective tissue containing numerous small, thin-walled blood channels, and occasional cells filled with blood pigment. The intima can no longer be differentiated from the completely organized thrombus. The media is of uneven width and its muscle fibers are in part replaced by connective tissue. There is no cellular infiltration to be seen in the media or the adventitia.

The microscopical section of a branch of the superior mesenteric vein (Fig. 85) reveals the lumen completely filled by a thrombus which is adherent to a thickened intima. The thrombus is only beginning to show organization where it adheres to the intima. At this site fine collagen fibrils run from the wall into the periphery of the thrombus, blending the transition so as to render it difficult to recognize the exact width of the intima. It is evidently composed of a very edematous young connective tissue, in the meshes of which many red blood cells are found. The internal elastic lamina is frequently broken transversely, but shows no tendency to fibrillar lamellation. The media is very edematous so that the muscle bundles are separated from one another. The adventitia, as well as the perivascular fat and connective tissue, is extensively infiltrated with polynuclear leukocytes and lymphocytes, which tend to invade the media.

The result of the gross and microscopical studies can be interpreted in the following manner: An old thrombosis had com-

pletely occluded the splenic and the portal vein, including its intrahepatic branches, and had undergone extensive recanalization. Lower in its course, the portal vein contained only an organized parietal thrombus, leaving an eccentric lumen, now occluded by a recent thrombus which is only beginning to undergo organization at its periphery. At this site the intima is markedly thickened due to new connective tissue production, the internal elastic membrane is broken but not lamellated, the muscularis of the media is interrupted by scars containing connective tissue and new elastic fibrils and the adventitia is extensively infiltrated with inflammatory cells which exhibit a perivascular grouping about the vasa vasorum.

We are obliged to conclude that the original thrombosis of the portal and splenic veins was caused by an inflammatory process in the wall. One can completely eliminate the possibility of phlebosclerosis as a factor because of the absence of any tendency to fibrillar lamillation of the elastica and by the presence of muscular hyperplasia. The thickening of the intima is only a reparative process designed to counterbalance the broken internal elastic membrane and the lesions in the muscularis.

The nature of the primary inflammatory process is more evident in the most recent lesion in the superior mesenteric vein. Here the destruction of the elastica and the media is already conspicuous and the inflammation is still in the acute stage.

From the microscopical evidence one can conclude that the process began years ago as a phlebitis of the splenic and the portal vein with subsequent thrombosis. That the inflammation was not entirely limited to the vessel wall is evidenced by the extensive thickening of the lesser omentum and of the periportal connective tissue arrears within the liver. Organization of the thrombus and of the periportal granulation tissue followed. The obstruction of the portal vein necessitated recanalization of the thrombus and of the adjacent tissue, leading finally to a spongy transformation of the involved area. But the phlebitic process had not been completely arrested, so that recently a recurrence occurred in the superior mesenteric vein which resulted in closure of the vessel and its tributaries.

In spite of our careful microscopical study, the etiology of the inflammatory process which initiated this sequence of events is still obscure. The histologic picture of the recent and the chronic stages of the inflammation is not specific. Bacterioscopic investigation failed to reveal the presence of visible bacteria. Stains for spirocheta were negative. The absence of inflammatory changes in any of the abdominal viscera make it unlikely that the infection of the wall of the portal vein had spread from them by hematogenous or lymphatic route, as is seen after appendicitis for example. It is conceivable that the splenic vein was the first to be involved, especially as it drains an organ which is concerned in the defense against infections. This conception of the pathogenesis of thrombophlebitis of the splenic vein and consequent splenomegaly was advanced long ago (Bonne), but it is impossible to prove.

In our case it is possible that syphilis may have been the cause of the phlebitis, for there is an old history of lues. Doubt is cast upon the rôle of syphilis by the entire absence of syphilitic lesions in any of the viscera.

DR. BAEHR: I am glad that Dr. Klemperer discussed the possible rôle of syphilis, as an etiologic factor, because I would now like to present a totally different viewpoint. Although this man had a history of having had a chancre thirty years ago, and although he presented Argyll-Robertson pupils and a positive Wassermann reaction, there were no gross or microscopical evidences of syphilis in any of the viscera, in the aorta, or in any other part of the vascular system.

This man was a Russian Jew who had been an excessive tobacco smoker. He regularly smoked at least two packages of cigarettes, ten cigars, and a number of pipes every day. He had been under observation for three years in our Out-patient Department for typical thrombo-angiitis obliterans affecting first one foot and then the other. Both the dorsalis pedis and the posterior tibial arteries of the right foot had been closed at one time. Eventually due to recanalization, the dorsalis pedis again became patent, but the posterior tibial remained permanently closed. At least one third of the cases of thrombo-angiitis ob-

literans at one time or other during the course of the disease suffer from migrating phlebitis. We have seen phlebitis migrans produce a primary thrombosis of the hepatic veins and it is not unlikely that it produced the primary thrombosis of the portal vein in this case.

Another thing is evident from the sections which were shown to you by Dr. Klemperer. Although the history of ascites only dates back four and a half weeks, the condition in the portal vein must be years old. It would take years to produce this type of lesion with recanalization and collateral hypertrophy of the vasa vasorum into good sized arteries. Thrombosis of the portal vein, especially the type which is produced by inflammatory disease of the wall can progress gradually and at first be parietal. It is often of this partially occluding type in migrating phlebitis of the extremities. Eventually, a gradual, slow closure of the vessel may take place, so that there is meanwhile time for the development of collateral circulation. By the time a complete closure of the portal takes place, collateral circulation is established. Subsequent recanalization of the occluding thrombus still further aids the circulation. Only after many years, when as the result of a new thrombotic process in other parts of the portal circulation—you remember that the superior mesenteric and many of its smaller branches were found at postmortem to have been recently thrombosed—only then did ascites develop. This may explain why our patient first noticed the increasing size of his abdomen only four and a half weeks ago. Finally, closure of many other small peripheral branches of the mesenteric veins resulted in the violent intestinal symptoms which preceded his death.

This brings up the last question whether the diagnosis of thrombosis of the portal vein could have been made. The patient's cachexia persuaded most of the clinicians to consider peritoneal malignancy as the more likely cause of the ascites. The appearance of a liver enlargement in the *x*-ray examination suggested to others the possibility of hepatic vein thrombosis. But the liver was never palpable, even after abdominal paracentesis, and *x*-ray reports of liver enlargement are often unre-

liable because of the difficulty of focusing upon an organ of this size and depth. The correct diagnosis should have been made, however, as soon as the violent diarrhea began, for in the presence of a painless ascites of obscure origin, the sudden onset of intestinal symptoms suggests an extension of the thrombosis into distal branches of the mesenteric veins of the small intestine.

CLINIC OF DRS. HENRY HEIMAN AND PHILIP COHEN

MOUNT SINAI HOSPITAL

PERIBRONCHIAL INFILTRATION IN CHILDREN

PATHOLOGICALLY and clinically pneumonitis can be classified into three types. The first is lobar pneumonia, most commonly caused by the pneumococcus, which is characterized by massive invasion of the alveoli and relatively little inflammation of the interstitial tissue of the lung. The second type is bronchopneumonia or lobular pneumonia caused by streptococci, pneumococci, and other bacteria, which is distinguished by discrete or, later, confluent areas of inflammation of a terminal bronchiole with its adjacent alveoli, and quite regularly, as Delafield pointed out, by an involvement of the framework of the lung. The third type is the so-called "interstitial pneumonia" in which we have a subacute or chronic inflammation of the interstitial tissue of the lung, rarely without, more commonly with a contemporaneous alveolar process, which is much less prominent than the interstitial part of the pneumonia. These types have been recently clearly described and differentiated, pathologically, clinically, and prognostically, by McNeill and his co-workers in England.

Studies in experimental production of pneumonia serve to shed additional light upon these different forms by showing their pathogenesis. The work of Blake and Cecil shows that with the exception of a pure influenza pneumonia, which exists only experimentally, the pneumonic process begins at the hilum of the lung. From here the bacteria, through the lymphatics, spread rapidly throughout the lobes by the way of perivascular, peribronchial, and septal interstitial tissue, quickly reaching the pleura. They make the statement that every pneumonia is

primarily an interstitial infection of the lung, the alveoli being secondarily invaded. The pneumococcus infection quickly leaves the lymphatics of the interstitial tissue to set up a solid, alveolar exudate. The Streptococcus haemolyticus, however, more than any other organism, has a predilection for the interstitial tissue of the lung, where the infection often lodges and persists. For this reason Blake and Cecil obtained in their experiments two types of streptococcus pneumonia, an interstitial type, when the resistance is good and the organisms few, and the broncho-alveolar, or lobular, type with which we are more familiar clinically. These divisions of streptococcus pneumonia have been studied pathologically from clinical material by several German writers, Steinhaus, Hecht and others, particularly after measles, and in America by Delafield and MacCallum. They all describe exactly what Blake and Cecil reproduced experimentally in streptococcus pneumonia, but interesting to note, all before these experimental demonstrations of the pathogenesis of pneumonia were made.

All these pathologists stress the frequency of interstitial pneumonia in streptococcus infections of the lung. MacCallum writes: "The change appears related in its origin to the peribronchial and perivascular lymph follicles. The interstitial changes arise very early in measles pneumonia, and distinguish it from croupous pneumonia. The distinction between the acute and the chronic foci of pneumonia lies in the presence of the leukocytic infiltration in the first, and the lymphatic infiltration of the second." All these papers have dealt chiefly with children, and I have found little referring to such bronchopneumonia in adults. Delafield recognized it in adults, but was chiefly directed to the disease in children.

Steinhaus and Hecht, in their articles, describe with great detail interstitial streptococcus pneumonia following measles. Both Steinhaus and Hecht review the entire previous literature on this subject, quoting numerous references. Hecht, in particular, stresses certain giant cells found, and shows the secondary though leading character of the streptococcus. He produced interstitial lesions similar to those of measles pneumonia by in-

jecting intratracheally metallic salts, or insufflating ammonia and ether, the latter shedding considerable light on postoperative or ether pneumonia. Steinhaus, like Hecht, depicts the various stages of interstitial pneumonia, the first being the stage of catarrh and atelectasis. In the later stages, as a rule, the alveoli are invaded, but not infrequently there is an interstitial pneumonic process with no alveolar exudation. "No clinical counterpart of such a pathology has been previously described. A pathology such as this would give no râles or tubular breathing, but would cause impaired resonance," and Steinhaus emphasized the chronicity of the lesion. In the later stages of peribronchial pneumonia there is a marked thickening of the interstitial tissues; more atelectasis, and in some cases organization and induration of the interstitial tissue. Once this has taken place the lesion and physical signs are likely to be permanent.

Winternitz, in this country, has also produced the lesions of streptococcus and influenzal pneumonia by intrabronchial insufflation of acid. This author has frequently commented upon the similarity of the pulmonary pathology of gas poisoning and influenza, the involvement of the interstitial tissues being a common and important factor. Similarly, foreign bodies like oils, coal dust, and zinc stearate set up an interstitial pneumonia. In the zinc stearate experimental pneumonia, an interstitial process without alveolar exudate was produced.

In lobar pneumonia, in accordance with the pathology, the classic physical signs are dulness, tubular breathing, increased transmission of voice and whisper, and râles at the onset and in the stage of resolution. In bronchopneumonia the signs are more variable, but râles are nearly always heard at some stage, and dulness is present if the bronchopneumonic area is sufficiently large. We thus often encounter discrete areas of dulness, bronchial breathing and voices, with or without râles, intermingled with normal areas of lung and foci where nothing but subcrepitant râles in varying numbers are heard. Because lobar pneumonia is an alveolitis for the most part, recovery is practically always quick, measured in days, except in those rare cases where

an interstitial process has followed. Since bronchopneumonia is composed of multiple broncho-alveolar foci with a prominent interstitial element, resolution is usually much slower and recovery must very often be measured in terms of weeks. Interstitial pneumonia, most commonly part and parcel of a so-called "bronchopneumonia," may simply be the end-result of such a bronchopneumonia, or the unusual sequel of a lobar pneumonia, or a separate entity, as when caused by gas and metallic poisoning, or by aspiration of foreign particles. In interstitial pneumonia the physical signs are dulness, diminished breathing and voice, and in extensive cases, signs of bronchial dilatation and retraction of the lung are present. Interstitial affections of the lung take months or years to heal, or may never completely disappear. We thus see a gradual increase in time of recovery in proportion to the interstitial involvement of the pneumonia, and see the difference in physical signs between lobar or alveolar pneumonia, bronchopneumonia, broncho-alveolar pneumonia, and interstitial types of pneumonia. We note that crepitant or subcrepitant râles are the sign par excellence of alveolar involvement.

With the above fundamental facts in mind we can better understand and appreciate a pulmonary syndrome which we have studied for the past five years. During these years, especially during epidemics of influenza and measles, we have encountered with an astounding frequency and great clarity of picture a clinical syndrome of dulness over one or both lower lobes of the lungs, diminished breathing, cough, and fever.

It must be emphasized at the outset that râles, breathing of bronchial quality, bronchophony or egophony, are conspicuous by their absence. These findings are contrary to the physical signs of pneumonia, lobar or broncho-, and are also different from the atypical pneumonias common in children. In atypical pneumonias small localized areas of dulness or râles alone are found, or even no physical signs are discovered. But the finding of a broad area of dulness on percussion, most often bilateral, is quite constant in our cases, with little quantitative, and no qualitative changes in breathing, and the audition of no râles.

This syndrome is frequently seen after the respiratory infection called grippe or influenza and measles. It then seems to be part and parcel of the disease, the invasion of the lung being contemporaneous with laryngeal and tracheal extension, and often accompanied by adenitis and otitis media. This has been proved by studies at the onset of measles of the lungs by Chadwick, Denton, Kohn and Koransky, and Bigler, the latter of whom reported the same findings in influenza and pertussis. It may be that in previous years we overlooked the pulmonary dulness through lack of light, fine percussion, which is essential in these cases, though at times the dulness is so marked as to suggest fluid or thickened pleura. If the pleximeter finger is snugly pressed against the chest wall, and light, almost faint percussion is made, called by some threshold percussion, we can practically feel the dulness with the pleximeter finger. The alternative opinion is, that owing to the frequency of influenzal infections since the epidemic of 1917–1918, and possibly because of some attenuation of the virus or changes in immunity, we are meeting a type of postgrippal pulmonary infiltration not previously present or noted. Our experience has been limited to children, but we have reason to believe the same condition exists, though less frequently in adults.

The children from the age of a few months up are usually brought to us, or referred to us, because of persistent fever, ranging around 100 to 101 F. in the evening, which cannot be explained, or because a distressing cough continues for weeks apparently without physical signs, which has been attributed to a "bronchitis." Examination reveals the dulness, most often in both lower lobes, particularly at the base and axillary regions, more marked on one side. That this dulness is not an artefact we proved to our satisfaction by comparison with the chest percussion of normal children. We also excluded the dulness due to atelectasis by the effect of deep breathing which removes the atelectasis due to habitually superficial breathing. We have thus far encountered very few cases with upper lobe involvement. The breathing is slightly or not at all diminished, and no other auscultatory or any other physical signs can be elicited.

As a rule the child in this, the post acute stage, feels well except when the fever rises to a relatively high level. The cough, dulness, and fever persist from weeks to months. We have many times seen the beginning of this pulmonary infiltration early in a grippe, and we then prognosticated the continuance of cough, fever, and thoracic dulness on percussion, either singly or in combination, for we have noted that the lesion is a subacute or chronic one. In the acute stage the systemic reaction is in proportion to the toxemia of the disease which is the precursor of this pneumonitis. This doesn't heighten the systemic reaction as the ordinary pneumonia does, but does succeed in prolonging the duration of the high fever, to be long continued as a low grade one. A few blood counts have been made, but shed little light on the picture, except to eliminate the diagnosis of typhoid fever. Either a slight or moderate leukocytosis with polynucleosis was found, or a normal blood picture in the later, protracted stages. These cases have had no further complications so far in our experience. They are exceedingly useful in explaining a previously inexplicable fever, some of which are undoubtedly attributed to other causes. The prognosis is excellent, for all our patients thus far have made a good recovery. Recurrences, however, are common but as a rule are milder in every respect, as to symptoms and signs. It seems to us that the lingering infiltration of the lung acts as a focus of reinfection akin to the endocardium or joints in rheumatic fever.

Although most of our cases have followed influenza and measles, it must not be thought that this is the sole etiology of this pulmonary infiltration. We very frequently see it after pertussis, scarlet fever, and upper respiratory infections, an observation corroborated by Bigler's pathologic and roentgenological studies. The impression we obtained from clinical studies, aided by a study of the bacteriology of the etiologic diseases, is that the peribronchial infiltration we are describing is probably caused by the Streptococcus haemolyticus, an agent which is known to have an affinity for the interstitial tissue of the lung, in which the lymphatics and blood vessels lie.

Since this type of peribronchial infiltration does not cause

death, we have no necropsy material to afford us an undoubted pathologic morphology. However, the prominent absence of signs of alveolar exudation and pulmonary parenchymal involvement have inevitably forced us to the conclusion that the pathologic process involves the extra-alveolar or interstitial tissue of the lung. This alone can account for persistent dulness with no other physical signs in so many cases. A study of the pathogenesis of pneumonia and the pathologic anatomy of the pneumonia of early measles which Denton and Steinhaus have proved is a pure peribronchial infiltration lends us the necessary

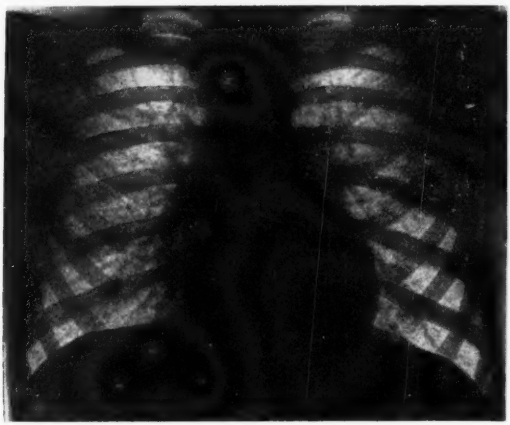

Fig. 86.—Case I (1/12/25): Marked increase of lung markings throughout both lungs.

pathologic background for our clinical syndrome of peribronchial infiltration. For the physical signs of our syndrome point to an extra-alveolar or interstitial process, of a low grade, subacute type, different from the usually accepted picture of interstitial pneumonia. It is for that reason and because it includes a broader and more accurate conception of the pathogenesis and pathology that we have preferred the term of "peribronchial infiltration." We may say here the peribronchial infiltration may be the first step to a broncho-alveolar pneumonia, when an

extension to the alveoli occurring in the early stages gives us the usual physical signs of a bronchopneumonia instead of a peribronchial infiltration.

From the pathology of this pneumonia we would not expect the *x*-ray to reveal striking shadows, as in lobar pneumonia. Fine lesions following the lines of the blood vessel and lymphatics, with increase of the lung markings, would instead be expected, or if the lesions were too small and not of sufficient continuity and thickness, the radiograph might be normal. We had *x*-ray pictures taken of 25 unselected patients who had peribronchial

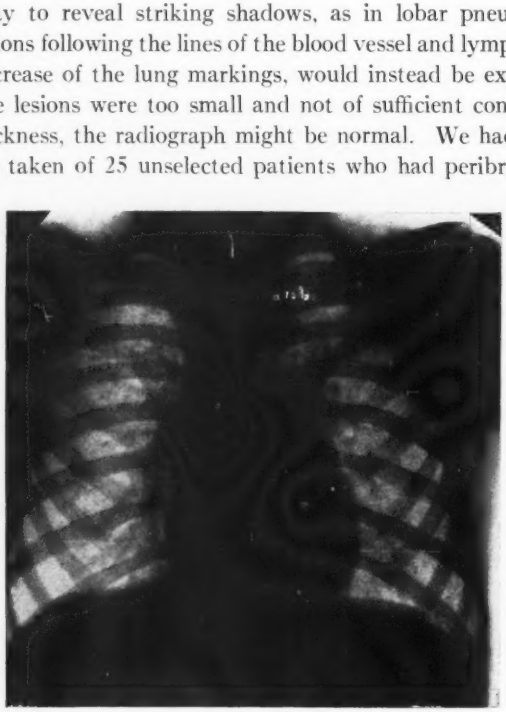

Fig. 87.—Case I (12/14/25): Improvement of chest after *x*-ray therapy.

infiltration. Technic is very important for overexposure will not reveal the shadow, and underexposure will not permit the shadow to be seen. Sometimes four pictures of a patient taken at the same time gave only one positive result, showing the importance of technic. The plates were submitted to three competent roentgenologists, and the number of positive readings varied from nine to fifteen, depending upon the conservatism of the reader in interpreting the lung markings, which is a moot

question among radiographic experts. One of them, Dr. Harry Wessler, went so far as to say that this indubitable dulness and a negative *x*-ray examination was more significant and diagnostic of the form of pneumonitis we are describing.

The type of lesion found by *x*-ray examination is that which Assman describes under grippe pneumonia, where he also discusses as a characteristic type, streptococcus interstitial pneumonia with especial involvement of the lymphatics of the lung. The later work of Chadwick and Bigler confirms this observation.

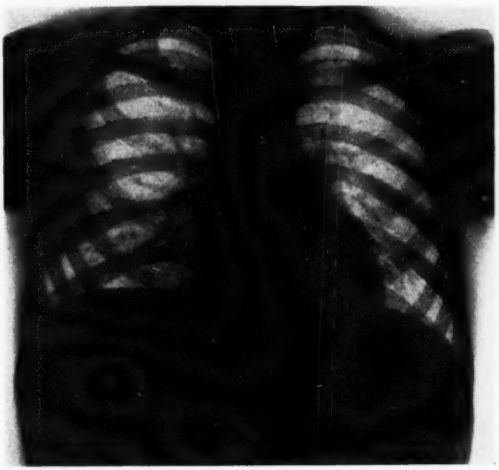

Fig. 88.—Case I (1/21/26): *x*-Ray picture of chest taken one month later Note decrease of lung markings from those of two months before.

Even when there has been a grippe streptococcus pneumonia with alveolar exudate, and confluent, but mottled, shadows on the *x*-ray picture of the chest, Assman comments upon the fact that resolution is always prolonged. After the mottled shadow has disappeared from the plate a veillike shadow remains for months in some cases, which is attributable to the residual interstitial pulmonary inflammation. Sometimes, as in many of our cases, this veillike shadow alone is seen, or merely an undoubted accentuation of the lung markings, which is common in influenza.

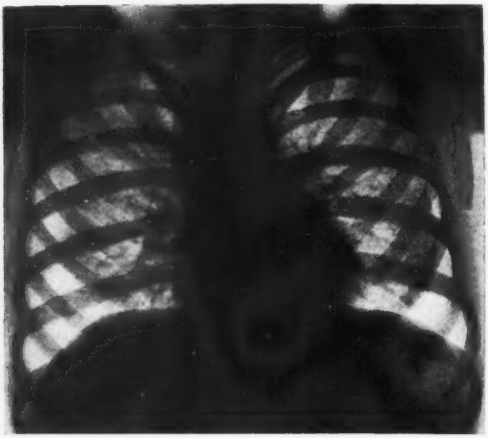

Fig. 89.—Case II (5/18/26): Infiltration of the right lower lobe; few strands at the left base.

Fig. 90.—Case III (9/8/26): Infiltration of right lower lobe and increase of markings in left lower lobe.

It may well be that the explanation of the steady increase in visibility of lung markings with the advancing age of the child is due to the imprint left on the lungs by recurring respiratory infection, a view also held by Bigler. Certain it is that the normal growth of the pulmonary vessels alone will not account for such striking differences of lung markings in children of the same age, and roentgenologists are now fairly well in accord with the view that normal lung markings are due to shadows the vessels

Fig. 91.—Case IV (2/4/27): Marked increase of lung markings with enlargement of hilar shadows.

cast. The fact is that because increase of lung striations is commonly seen, their significance and value are discounted as not being pathologic, just as formerly solitary dulness of the chest on percussion was relegated to the field of normalcy, because of lack of associated signs. Our investigations cast considerable doubt on these *x*-ray and physical diagnostic interpretations.

Very recently Wasson of Denver described the same clinical and *x*-ray pictures with the identical pathology as we ascribed

to peribronchial infiltration. He believed that sinusitis was the usual cause or concomitant factor and hence called the syndrome bronchosinusitis. We do not agree with this conception of pathogenesis or the necessity of a concurrent sinusitis but in all else, and especially with his interpretation of lung markings and their exaggeration, we are in accord.

The diseases from which peribronchial infiltration has to be differentiated are typhoid, tuberculosis, pyelitis, bacteremia, and

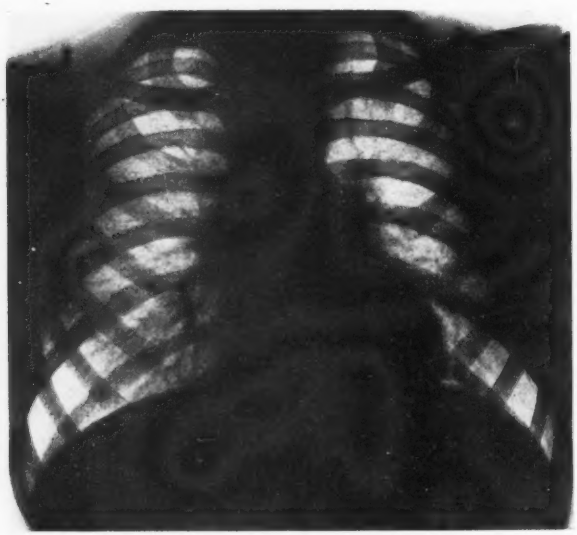

Fig. 92.—Case V (4/6/28): Increase of lung markings with filling in of cardiohepatic angle with markings.

uncomplicated influenza. We may add here, however, that in 2 cases of typhoid fever we discovered the dulness of peribronchial pulmonary infiltration. It is our belief that the cases of influenza previously described as characterized by a febrile period of six weeks or longer were complicated by the pulmonary condition we have found. Many cases of so-called "postinfectious pyrexia" are due to this syndrome.

The prognosis is always excellent. Either the chest becomes

normal in a few weeks, or, if the interstitial tissue of the lung becomes indurated and replaced by fibrous tissue the dulness may become permanent, though with no ill effects, as far as our present knowledge permits us to say. It may well be that some of these cases with chronic dulness go on to the stage recently given the title of "The Damaged Lung." At all events, though the pulmonary lesion is a complication of an acute infection, it tends to be a chronic one as shown by clinical evidence, the chest examination, *x*-ray evidence, and pathologic studies.

The treatment is fresh air, heliotherapy, and in some chronic cases, *x*-ray therapy, which is therapeutic both for the lymphocytic infiltration and for the fibrous replacement of the interstitial tissue. Internal medication is of no avail in this condition. Diathermia has never been invoked by us for these cases, but judging by the reported good results in cases of unresolved pneumonia, may be of value in this condition. Ultraviolet radiation is of very doubtful value.

CONCLUSIONS AND SUMMARY

1. An atypical but frequent pulmonary complication has been encountered by us for the past five years.

2. This syndrome consists of dulness on percussion, usually over both lower lobes, often in the axillary regions, low grade fever, for a long period from 100 to 101 F. as a rule, and in most cases cough. Râles, bronchial breathing, or changes in voice were conspicuous by their absence.

3. The above picture is a complication of grippe or influenza, measles, pertussis, scarlet fever, and other upper respiratory infections.

4. Although the course tends to be chronic, we may find the pulmonary involvement early in the course of the primary disease. It then serves to prolong the higher fever and toxemia of the initial infection.

5. In the chronic stages the patient suffers little, for the fever is not high, but at times the cough is distressing.

6. Recurrences are common because the focus of chronic

infection in the lung sensitizes instead of immunizes the patient to colds.

7. The recognition of this syndrome is useful in accounting for many coughs and fevers, previously inexplicable, some of which have been formerly termed "postinfectious pyrexia."

8. A study of the pathogenesis and pathology of pneumonia lead us to believe that the pulmonary syndrome we are describing is a streptococcus pneumonia of the interstitial type, without alveolar exudation. This form of pneumonia is not uncommon in children.

9. The interstitial lesions may completely resolve after a long time, or become indurated, causing a permanent dulness on percussion of the region affected.

10. *x*-Ray studies have shown fine infiltrations in some of our cases, with accentuation of the lung markings in the others.

11. The prognosis is excellent. There were no deaths in our cases, and no children suffered from deterioration of general health.

12. The treatment we followed was fresh air, heliotherapy. and *x*-ray therapy in protracted stubborn cases. Opiates were given to relieve the cough.

CLINIC OF DR. JOSEPH EIDELSBERG

DEPARTMENT OF ENDOCRINOLOGY, NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL

ENDOCRINOPATHIES: THE THYRO-PITUITARY SYNDROMES. DIAGNOSIS AND TREATMENT

THIS morning we shall present a number of patients from our Endocrine Clinic, but before doing so, let us review a few fundamentals. The endocrine glands, taken as a whole, have in common a number of functions—and disturbances in these functions, of one, or more, or all, give us the clinical pictures by which we recognize that the individual patient belongs in our realm. These functions which the various glands of internal secretion possess are as follows: First, control of growth; second, control of development; third, control of sex characteristics; fourth, control of metabolism, basal rate, fat, sugar, calcium, phosphorus, etc.; fifth, a relation to or control of the autonomic nervous system; sixth, a relation to or control of the hematopoietic system; seventh, a relation to or control of mentality; eighth, a relation to or control of behaviorisms and character.

There are probably other functions which the endocrine glands exert concerning which we have much to learn.

Thus, if the patient before us presents disturbances, whether they be an arrest or regression, on the one hand, or an exaggeration, on the other hand, of growth, development, sex characteristics, and so on, we recognize that the pathology must lie in these so-called "endocrine glands." We must also keep in mind that these various glands, the thyroid, the thymus, the parathyroids, the anterior pituitary, posterior pituitary, the pancreas, the interstitial glands, the adrenals, and the others work hand in hand, each having an effect on the other, so that

when one fails, or overacts, the end-picture resulting is a pluriglandular disease and not monoglandular. In the beginning of the disease one gland may be primarily at fault and may even be the only outstanding seat of pathology throughout, or, several glands may be at fault from the onset. In treatment, the presence of these other disturbed glands must be taken into consideration, and the ideal treatment must often be pluriglandular in nature.

Many times in the past ten years that this clinic has functioned we have proved this theorem. Patients young and old, presenting apparently simple syndromes, for example, cretinism or myxedema, when treated as monoglandular diseases, have improved to a certain extent, but extensive search for further glandular involvement would suggest a further attack from another angle, and new and further improvement or advance would follow. The cases to be shown will exemplify and emphasize this contention. Two glands, the thyroid and the pituitary, are the ones we will particularly interest ourselves in this morning.

The thyroid gland has a number of functions. Its most commonly known function is the control of the rate of metabolism, but with other glands it enters into the control of sex development and characteristics, sugar metabolism, a detoxification of end-products of metabolism and infectious toxins, development of the osseous and nervous systems and so on.

The pituitary gland is regarded by us as two separate glands: We speak thus of the anterior pituitary gland and the posterior pituitary gland. Further, the anterior gland has two (or more) separate functions: (1) Control of growth and (2) control of sex characteristics, and we can have a disturbance of one or the other or both—one may be increased and the other decreased. The posterior pituitary gland has a number of functions, among them (1) control of metabolism; (2) control of sugar metabolism (directly opposed to insulin in action), and in characteristic deficiency giving the exaggerated increased sugar tolerance curve (even flat or the so-called "plateau curve"); (3) maintenance of blood pressure; (4) oxytoxic function; (5) a control of fat met-

abolism characteristic deficiency giving the girdle obesity, and so on. We can have any one of these functions affected—increased or decreased, or any combination of disturbances—so-called "dispituitarism."

These two glands, the thyroid and the pituitary, are frequently affected in the same patient, giving us the so-called "thyropituitary deficiency syndromes," and we will dwell further on this particular phase in this hour.

Fig. 93.—Patient F. S. (Case I). Age seven years. Showing outward manifestations of thyropituitary deficiency syndrome.

Case I.—The first patient, F. S., a girl, is now about seven years of age, brought to us about six months ago. She has a brother and a sister, ages five and ten years, both normal children. The mother and father are healthy. As an infant, following a normal birth, the mother noticed that she was extremely constipated, her cry was peculiar and "nasal," and that she nursed with extreme difficulty. Even at the age of eighteen months her head would

fall from side to side; and she first sat up at twenty months. Her first teeth appeared at about two years. As time progressed it was observed that she was distinctly mentally deficient. Before you, one sees a girl about seven years of age—but appearing much younger. She is about 3½ feet in height, and weighs about 42 pounds. She is pale, her skin is very coarse, dry, and thick; her hair is coarse and dry, she stands with shoulders stooped, mouth open, and takes little interest in her surroundings. As you will notice her eyes are rather widely separated, and her nose is the so-called "saddle-back type." Her body is covered with a growth of lanugo-like hair. Her gait is especially interesting—she walks as though her feet are glued to the ground,

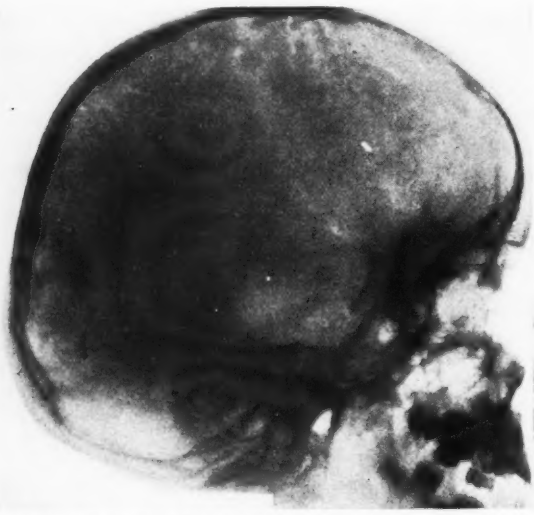

Fig. 94.—Patient F. S. (Case I). Profile *x*-ray of skull, showing a sella turcica about one half the normal size.

her toes are never raised, and consequently we can understand her parents complaint that she rapidly wears through the tips of her shoes. She has a slight umbilical hernia, which was more striking some months ago. Please remember that her entire picture was much more marked six months ago. She has an almost spontaneous Babinski, and exceedingly exaggerated knee jerks, and an ankle clonus, elicited now with great difficulty, although produced very readily up to two months ago. She could hardly walk unassisted, although today she can get about more easily, though still peculiarly. The important laboratory findings are as follows: Basal metabolism rate originally was about −20 per cent, with an average rectal temperature of 97.2 F., and an average pulse rate of 72. Her urine was normal and blood count

showed a slight anemia with a white cell count of about 5000, and a differential count of about 55 per cent lymphocytes, and 53 per cent polys. Our impression, as yours probably is today, was that we were dealing with a more or less marked hypothyroid state, a type of cretinism. Thyroid was administered for three months up to 7 grains daily with slight improvement. Then three months ago we discovered that *x*-ray of her skull revealed a sella turcica less than 50 per cent of the normal expected size, and the sugar tolerance curve was of the so-called "flat or plateau type." It was then that pituitary substance was added, and for three months now she has taken the following: Thyroid gland, 3 to 5 grains and pituitary gland, 12 to 20 grains daily, and the rate of improvement increased definitey.

Fig. 95.—Patient F. S. (Case I). *x*-Ray of sella turcica—small, but otherwise no abnormalities.

In résumé we would say she was a type of thyroid deficiency, with some neurological signs and symptomatology (so-called "thyroneural dystrophy") due to poorly and incompletely developed nervous tissue, a result of insufficient thyroid hormone, during fetal life—with a superimposed bilobar pituitary deficiency. On proper therapy she has improved, and is continuing to do so. The future is not entirely bright, but we have followed

such children several years who are now able to obtain some education and become self-supporting, and in some cases are indistinguishable from their more fortunate brothers and sisters.

Case II.—The next patient, C. C., a female, is eight years of age. She has one sister aged sixteen, and one brother aged ten, both well. Her mother and father are well, but are first cousins. She was born prematurely (at the seventh month), due to a "placenta praevia," and weighed less than 3 pounds. Unable to nurse, she was fed with a dropper, spoon, and bottle, and when two years old her weight was only 9 pounds. Her first tooth appeared at about a year, and she did not walk before she was about three years of age.

Fig. 96.—Patient C. C. (Case II). Age eight years. Showing apparent external manifestations of an endocrinopathy pluriglandular deficiency—thyropituitary thymus syndrome.

Fig. 97.—Patient C. C. (Case II). Note facies, epicanthus, narrow shoulders, etc.

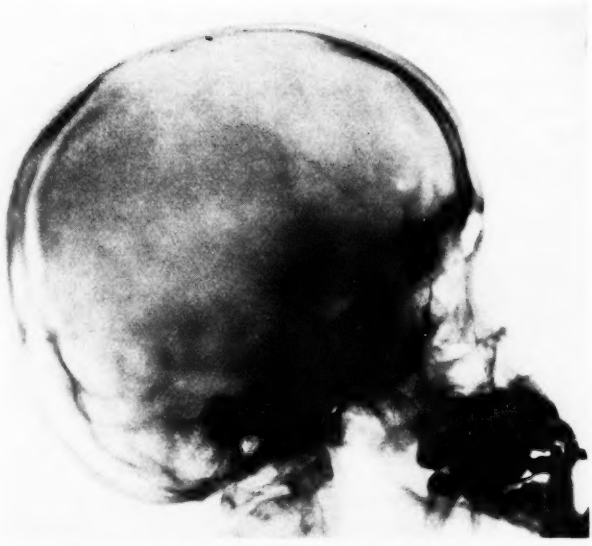

Fig. 98.—Patient C. C. (Case II). Profile of skull.

Fig. 99.—Patient C. C. (Case II). *x*-Ray of sella turcica—small (50 per cent undersized), but smooth.

When six years of age she was rejected by the school autnorities as being mentally deficient. From then to date she has rapidly gained weight (60 pounds on first examination five months ago). In addition, she walks slowly, barely raising her toes from the floor. Her retarded mentality is very evident. Her hair is scanty and coarse. Her skin is coarse and seems edematous, but does not pit on pressure. Notice the looseness of joints, and the hypotonia and hyperextensibility everywhere. She has a slight epicanthus and the eyes are rather widely separated. Her tongue is thick, heavy, and

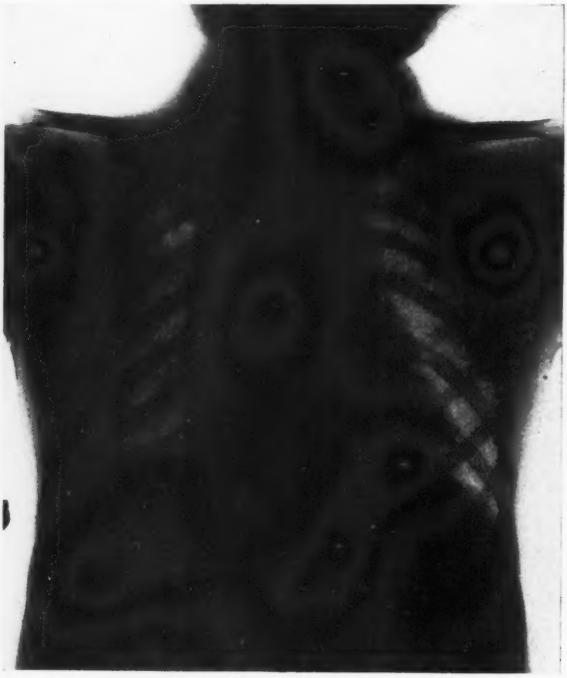

Fig. 100.—Patient C. C. (Case II). *x*-Ray of chest. Note width of thymus shadow.

coarse. Her shoulders are narrow. Percussion over the manubrium reveals a dulness extending about 1½ inches to either side of the midline. She stands with shoulders drooped, and as you notice her movements are choreo-athetoid. Her back is covered with a growth of lanugo-like hair. She is "pot-bellied." Her reflexes are all exaggerated and an ankle clonus, though slightly present today, was originally exceedingly positive. There is marked dermographia. The other physical and laboratory findings are also interesting. Her tem-

perature, originally between 97.4 and 98 F., has lately become 99 F. Her pulse has increased from 80 to 110. Blood Wassermann is negative. Sugar tolerance curve is of the plateau or flat type. *x*-Ray of the sella turcica reveals it to be smooth in contour, no evidences of erosions or pressure atrophy, but more than 50 per cent undersized. Her chest *x*-ray shows a rather extensive infiltration throughout the mediastinum—the mass measuring about 2½ inches in diameter and extending almost the full length of the mediastinum. The basal metabolic rate was −19 per cent.

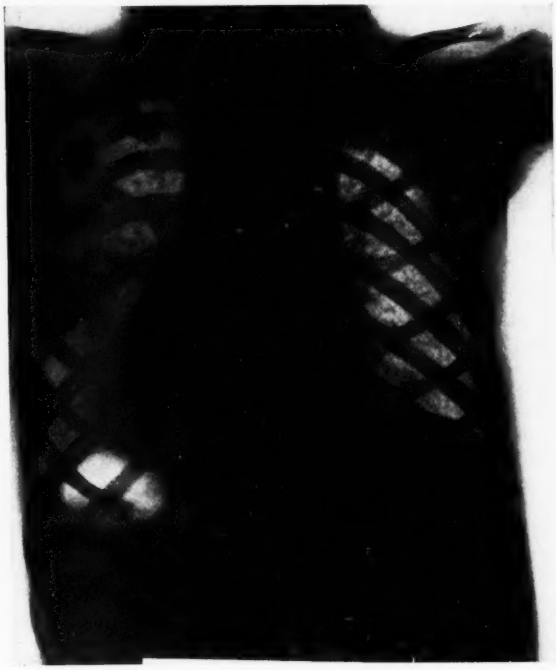

Fig. 101.—Patient C. C. (Case II). *x*-Ray of chest, showing width of thymus shadow, about one month after preceding *x*-ray.

As we readily see, we have a syndrome of mental retardation, associated with a thyroid and bilobar deficiency with a large thymus. The neurological findings are a result of a deficiently developed nervous system—so-called "thyroneural dystrophy," as in the previous case. The treatment includes the adminis-

tration of thyroid gland by mouth, sufficient to raise the basal metabolic rate to about 10 per cent above the average normal —an average of about 5 grains daily; pituitary substance by mouth (about 15 to 20 grains daily) and by injection, antuitrin and pituitrin. Finally, *x*-ray therapy for the large thymus gland. All this has been begun, and we must continue it for a long time, urging patience on the part of all concerned, for only with persistence can improvement progress. Again, we emphasize the need of polyglandular treatment, and not monoglandular.

Case III.—The third patient, W. H., is a boy, eighteen years of age. He came to us about eight months ago, with this history. His birth was normal, at full term, and his infancy and early childhood negative except for the usual illnesses—measles, scarlet fever, and diphtheria. At about the age of thirteen years, his parents noticed he was not developing normally. Although his brothers both entered high school at thirteen years of age, he was only in the seventh grade. He was slow in his movements, "lazy," and was gaining weight rapidly. At eighteen years he weighed 170 pounds though only 5 feet, 2 inches in height. There was no growth of hair on his entire body-even his eyebrows being very thin, the outer third almost missing. In addition he had had convulsions during the previous year, averaging one or two a month. These were of short duration (five to six minutes) and comparatively mild. His parents were also concerned because he had an infantile penis, and his breasts were growing. Though modified somewhat by treatment we still see today plainly the earmarks of his endocrinopathy: the complete absence of hair, facial, axillary, abdominal, and pubic; the female-like breasts, the large pubic pad of fat, the lower abdominal and pelvic obesity, the small lateral incisors, the scanty eyebrows (especially the outer third) the small hands, and tapering fingers. Note the "acorn-shaped" penis. His study further revealed: (1) A basal metabolic rate originally −21 per cent; (2) a flat sugar curve; (3) blood pressure averaging 86 systolic and 50 diastolic; (4) rectal temperature between 97.2 and 98.2 F.; (5) a sella turcica about one third less than the average expected size. We began energetic treatment with pituitary gland substance, 30 grains whole gland by mouth daily, and $\frac{1}{2}$ cc. each, antuitrin and pituitrin, by injection daily. In the following three months he lost 10 pounds, and had had only two convulsions. At this point thyroid gland was added, increasing the dose to 5 grains daily. Since he has had no convulsions, has brightened considerably, and today his weight is 142 pounds. Treated as a hypopituitary syndrome he had improved slowly, but regarded as a thyropituitary deficiency syndrome we began to obtain a result almost beyond our hopes and expectations.

Diagnosis and Treatment.—In making our diagnosis of these syndromes, we consider the various glandular components

separately. The thyroid deficiency is considered a possibility if we find several, or more, of the following earmarks: coarse, scanty hair on the head, lanugo-like hair on the body, "saddle

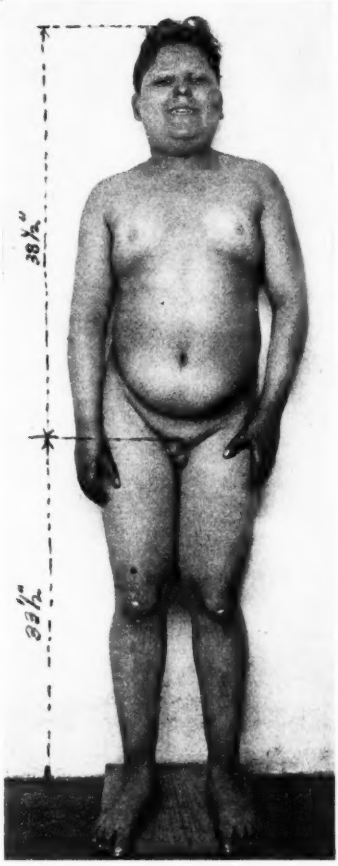

Fig. 102.—Patient W. H. (Case III). Age eighteen years. Showing the externally visible manifestations of a thyropituitary deficiency syndrome.

back type" nose, large tongue, pot-belly, umbilical hernia, subnormal temperature, thick coarse pale skin, constipation, and

a basal metabolic rate below −10 per cent. The number of these stigmata found in any one case depends on the degree of deficiency and its duration. Were we to err in treatment, we have always felt it should rather be an error in administration, rather than one of omission, because occasionally therapeutic trial makes the diagnosis by its results. I have yet to see any distinct harm in a patient where thyroid substance was given thus.

In considering the possibility of pituitary gland involvement, we always regard it as two separate glands, namely the anterior pituitary gland and the posterior pituitary gland. Although the cases presented today were examples of bilobar deficiency, we may have either lobe affected alone. Thus, anterior lobe deficiency is indicated by the lack or arrest of growth, small extremities, small tapering fingers, and deficient sex characteristics, primary and secondary, such as small genitalia, amenorrhea, small breasts, absence of hair, etc. The posterior lobe involvement is suggested (1) by the girdle, lower abdominal or pelvic obesity (in characteristic cases); (2) by an increased sugar tolerance curve—our typical cases giving us frequently the flat curve when 1.75 Gm. of glucose is given per kilo of body weight; (3) low blood pressure; (4) reduced B. M. R.; (5) occasionally, the syndrome of diabetes insipidus. We use the *x*-ray only as an added diagnostic aid—when tumors are present we find the enlarged, irregular outline, with erosions, atrophy, and so on; and when the sella turcica is distinctly small (its diameter being less than one fifteenth of the skull diameter), or when it is enclosed by bridging of the clinoid processes, as a possible indication of decreased pituitary size and decreased function. The perimeter occasionally gives us the clue by disclosing the limitation in the fields of vision (for colors early) in tumor cases. However, our cases this morning were examples of simpler hypofunctions of the nontumor type. We have avoided thus far pointing out the characteristic measurements and growth disturbances, but the last case (W. H.) shows it very well. The usual normal has a more or less equal measurement from the symphysis pubis to the top of the head, and from the symphysis pubis to the sole of the feet. In this patient you will observe he

measures 38½ inches from his symphysis up, while it is but 33½ inches from his symphysis down. If you will measure Case I (F. S.) now (although younger and at this age the normal upper half is larger than the lower half) you will find a marked difference—24 inches from the pubis up, and 18 inches from the pubis down, much greater than it should be at this age. The lack of the anterior lobe hormone arrests the growth of the long bones, as the femur, tibia, and fibula, producing this disturbance in the

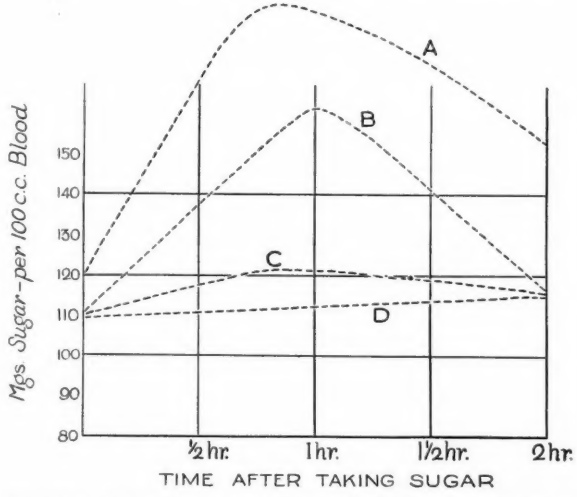

Fig. 103.—A, Type of curve in hyperthyroidism, hyper-posterior-pituitarism, decreased tolerance curve. B, Normal curve. C, Increased tolerance curve. D, Markedly increased tolerance curve. Curves C and D (flat or plateau curve) found in hypo-posterior-pituitarism and in hypo-adrenia.

ratio. Likewise, the span from fingertip to fingertip, instead of being about equal to the height is less, and in the case (W. H.) it measures about 60 inches (the height being 62 inches).

As to treatment, we feel the general tendency is to "undertreat" these cases. Thyroid is given in the younger patients, where basal metabolism determinations are impracticable, until the rectal temperature is raised above 99.6 F. In the older patients thyroid is administered until the pulse rate, when the

patient is at rest, is 96 or above, and an even better guide, until the basal metabolic rate is at least +6 per cent. We have seen patients who have needed as much as 15 grains of thyroid gland a day—and these patients had been receiving 6 grains per day before. It was no surprise that the improvement was not obtained on the smaller dose, though distinct improvement was obtained on the larger dose.

The pituitary gland substance is ideally administered by mouth and by subcutaneous injection. The anterior lobe substance is given in doses varying from 15 to 45 grains daily. The whole gland substance is administered in doses varying from 12 to 40 grains daily. We also give extract of the anterior lobe substance by injection, 1 cc., in extreme cases daily, in milder cases two or three times a week. If posterior deficiency is marked, posterior lobe extract is given by injection, in $\frac{1}{2}$ cc. doses, or larger, daily, and in milder cases two or three times a week. Our best results are obtained by the combined methods of treatment. We have taught many patients to administer the injections for themselves, just as many diabetic patients give themselves insulin.

Prognosis.—We have always felt that if we could get these unfortunate patients started on sufficient therapy early in life, in infancy, childhood, or even in adolescent period, much can be accomplished. Many have come to us in adult life. Still we have succeeded with apparent hopeless problems—and, of course, failed many times. There is always much to be gained, and nothing to be lost. Many patients who were started years ago by us, today are quite presentable, of fair or good intelligence, appearance, and functions. Many have failed to progress or improve, but if we redeem but one in ten, or even more attempts, we have done some good in our stay on this earth—while in truth our percentage of improvements is far better.

CLINIC OF DR. C. WARD CRAMPTON

POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL AND WEST SIDE HOSPITAL AND DISPENSARY

SYNTHETIC DIAGNOSIS

IN several ways, the health examination has made a contribution to medical practice. It has opened the door to the wide and long vista of preclinical diagnosis and treatment, and preclinical medicine is a field which promises the solution of many of our problems. Its most immediate service, however, lies in the demonstration of the value of "synthetic diagnosis." This is a term which, to the writer, most aptly expresses a general principle in medicine. It is important enough to warrant definition and illustration, which accordingly is undertaken as follows:

The health examination is a survey of the whole man. It may be brief or long; good, poor, or bad; impressionistic or meticulous; but it is still a survey of the whole man in an endeavor to determine, study, and to further his health. It may be restricted to the search for signs of illness, but it goes over the whole body; it may include a study of heredity, previous illness, present manner of life, anatomical measurements, and physiologic tests in an effort to make a complete survey. It still goes over the whole body and neglects nothing. The diagnostic product of the health examination is something which has the savor of a novelty in medicine. It is, first, the collective statement and evaluation of pertinent facts, from the fields of anatomy, physiology and pathology, and the like. It is, secondly, a study and statement of the relation of these facts to each other so that, thirdly, and to the purpose in hand, a synthesis may result in a concept of the man as a whole with reference to his health upon which treatment may be securely founded. This is "synthetic diagnosis."

The traditional process of diagnosis is a process of isolation. It is intensive. By observation, exclusion, and judgment, the disease from which the patient is suffering is finally disclosed. Traditional diagnosis is complete when for example, one may say with truth, "The patient is suffering from myocarditis." Such a diagnosis commonly degenerates into a statement that, "This is a myocarditis case." It focuses the full attention of all upon the disease as an entity, and the patient is in danger of becoming a nonentity.

A synthetic diagnosis includes, first, the sum of several intensive diagnoses, as many as there are pathologic conditions which can be found. This is quite different from the monodiagnosis described above. It may be called a polydiagnosis.

Case I.—S. H., a married, childless woman of thirty-one, who had formerly been diagnosed as "nervous." The following is a list of the pathologic findings:

Chronic sinusitis.
Infected tonsils.
Psychoneurosis.
Arterial fibrosis.
Chronic pyelitis.
Chronic cystitis.
Intercostal neuralgia.
Autonomic instability.
Pathologic introversion.
Uterine retroversion.
Dental apical infection.
Postinfluenzal anemia and asthenia.
Cholelithiasis.
Asthenopia.
Protein sensitive.
Colitis.

This list of diagnoses is a part of a synthetic diagnosis. It illustrates the fact that several related or unrelated pathologic conditions can, and do occur at the same time. The number will seem large. Women of thirty-one frequently show from three to twenty noteworthy diagnoses. The number increases up to the age of fifty or so. Yet, this list is incomplete for it omits a number of less clearly defined conditions which might be included, and would be included if the diagnoses were made by a series of

specialists instead of one observer. But of course, this list is not a complete synthetic diagnosis. Each item is worthy of consideration. Every one affected the patient. Yet, each item would warrant our calling the patient a "case" of sinusitis, cystitis, colitis, etc.,

This patient had been treated for anemia, nerves, psychoneurosis, and constipation by four different physicians. She might easily have been treated by as many more who would be satisfied to confine their attention to one single field. The cure of most of these conditions would be difficult, unlikely or impossible if undertaken alone. The cure of one of these conditions would have satisfied a professionally myopic specialist, but it would have left the patient unhealed and unserved. Medical science, as a science, would not have been employed in her behalf. This monodiagnosis is giving way to polydiagnosis, the first step in synthetic diagnosis.

The next step is evaluation of the grade, influence, and importance of each item on the list introducing the element of quantitative diagnosis.

The next step is the observation of the relationship of the items of the list. They may be related to each other as father and son, or as brother and sister. Both parents may be present, and a grandparent may appear. In other words, the cause and result may be present, two causes and one result, or two results of a common cause or causes, unto several generations. There may be as many interrelations as may occur among the natives of a small South Sea island. One must not expect to find all the causes present in the list. Some may have disappeared (past illnesses), others may be present in other categories (heredity, environment, habit, function). For example:

Direct Causes.—The pyelitis gave a pure culture colon bacillus. It cleared up quickly and remained clear when the treatment for the colitis reached a point of efficiency. Although other direct and indirect means of treatment were employed it is probable that the colitis was in parental relation to the pyelitis. The intercostal neuralgia cleared up two weeks after the infected teeth were extracted. The teeth were nonvital. They showed no signs

to the *x*-ray, but did show a shadow on transillumination, and cultures showed Streptococcus viridans. Though local and other general measures were used on the neuritis, it is probable that the teeth infection was one of the causes. The sinusitis, tonsil infection, colitis, and colonic stasis no doubt contributed. The making of a list of pathologic conditions is an essential in the proper study of the relationships of each condition to the other, finding causes and planning treatment.

It is clear from the above that the treatment of one condition aided the cure of the next. Curing the colitis aided the cure of the pyelitis or actually cured it. This is frequently the way that patients are cured and medicine gets a reputation for healing a part of the body they never reach directly. Much of our empirical medicine has been of this type.

As a corollary, however, if one does not find and cure the cause, the direct attack on the disease when it is located is often futile. The colon bacillus pyelitis resists local antisepsis with great tenacity and it can be "cured" as many times as a gastric ulcer. Rheumatism and intercostal neuralgia may be treated locally by physiotherapy, by iodine, salicylates, with injections of many varieties of vaccines and proteins, and internally by the whole pharmacopoeia, but unless the original nests of streptococci are removed and their colonies eradicated, there is no cure. This seems, at this stage of medical development, almost axiomatic, yet there is still much evil done by treatment of results and neglect of causes. It is characteristically monotreatment, perpetuated by monodiagnosis.

Polydiagnosis, in addition, aids the physician to avoid the similar error of treatment of symptoms instead of disease. It is easier for the best physician to slip back a few decades, listen to the complaint, write a prescription, and ring for the next patient. The hard route of modern medicine demands record, search, and research. It always rewards the physician, the patient, and the profession.

Principles. No disease is independent of another co-existing illness. No organ of the body is independent of any other. No illness is an isolated phenomenon. A full knowledge of accom-

panying diagnostic facts places the specialist or the general practitioner in a position immeasurably superior to the mono-diagnostician or the monotherapeutist.

Concrete examples of the advantage of a synthetic diagnosis may be found every day, in every patient by every physician. The following excerpts from case histories each illustrate a principle:

Case II.—A man of thirty-nine, C. C. Pains of diverse character in the gallbladder region with tenderness and increased muscular tension. Sulphanilic test negative. Gallbladder visualization inconclusive. Gastro-intestinal hypertonicity marked and variable. Moderate colitis. A gallbladder operation had been recommended and approved by consultant. Among a variety of impairments discovered was a large inguinal ring on the right side, with impulse but no protrusion under ordinary conditions. It was suspected of being the cause of the "gallbladder disease." It was. In an operation under spinal anesthesia, as adhesions about the adherent omentum were broken up, the patient remarked, "There, that pain is gone. I hope it stays away." It has, for eighteen months.

Principle.—So long as there is an autonomic nervous system, a symptom may be far distant from its cause, and neither the epigastric pain in appendicitis nor the appendicular pain in pneumonia is the only diagnostic example thereof.

Case III.—A man of thirty, H. C. Fractured larynx, infected, and a sinus discharge despite two years of local and operative treatment by competent laryngologists who treated the larynx and the larynx only. A variety of pathologic conditions were noted and treated and various physical processes were toned up. The larynx was left relatively alone. The man got well, his larynx improved, and in four months returned to normal function. He resumed his duties as a waiter, calling orders to the kitchen.

Principle.—If you cannot cure the disease, cure the man. Perhaps he can cure it himself.

Case IV.—A man of sixty-two, L. M. In generally fair to poor condition of heart, arteries, kidneys, blood pressure, with edema of the legs, etc. A large and growing prostate, bacteriuria, and an increasing residual urine. He was put into good condition from seborrhea sicca to the pes planus. The urine cleared up but the prostate continued to increase in size. Suprapubic operation was done. The patient was up in four days, left the hospital in eight days, resumed work promptly.

Principle.—Both the surgeon and the patient appreciate the fullest cooperation that the body (and mind) of the patient can be made to give. This sometimes makes the final decision.

Cases V to C.—Patients suffering from myocarditis, nephritis, diabetes, etc., in poor condition from a collection of disabilities which were modified or removed, thereby giving the affected organ vigorous and continuous cooperation.

Principle.—Perhaps this is the best "treatment of a chronic disease." If a man is burdened with packets of lead in every pocket which can be removed, how much better can he bear the burden on his back, which, perchance, we cannot lighten.

The polydiagnostic list, therefore, helps to find simple, direct causes. This permits shortcut, direct treatment. It permits treatment of two conditions to support each other. It helps the development of an harmonious therapeutic program.

Further analysis will indicate groups of illnesses related to each other by *origin*, *sequence*, *kind*, and *location*.

Grouping by *origin* is illustrated by the bacterial infection group.

Grouping by *sequence* is a fascinating and fruitful occupation, frequently leading back out of our clinical list far into the preclinical field. The intercostal neuralgia may have for its antecedent the infected teeth and tonsils in which the colitis may have played a rôle, and behind this the autonomic instability, asthenia, bad nutrition habits, and the psychoneurosis. This process of linkage into a chain of causes and results, the present state of science does not permit to be exact. It can only become exact by the employment and testing of this method of analysis. This reaches back into the preclinical field. We, as physicians, customarily see only terminal phenomena—the X Y Z of the preclinical-clinical alphabet. With the study of preclinical medicine we hope to make progress back toward the A, B, and C. So much for grouping by sequence.

As to *kind*, one may make groupings under the head of fibroses, hypertrophies, asthenias, hypertensions, and perhaps gain some profit and understanding.

As to *locality*, we find the gastro-intestinal group and the circulatory system are represented. The endocrines show directly and indirectly, the autonomic nervous system appears in several numbers, while the mental field is strongly to the fore.

In each diagnosis the medical enthusiast will see the influence of his own special interest cropping out and explaining everything. The medical specialist of the older myopic type will see nothing but the one thing in which he is concerned; for him nothing else will ever exist. The modern specialist will see item after item of significance, aid and guidance. After a decade or so he will ask for the synthetic diagnosis as a routine procedure.

But a list of pathologic conditions, valuable as it is and may be, is only a polydiagnosis. There are other considerations of importance to complete the synthesis.

Anatomical structure and **measurements** reveal data that the anthropologist, the physical trainer, the endocrinologist, and the students of constructive medicine have been endeavoring to tell the clinician for many years. A few selected measurements and observations have place in the diagnostic routine. These include weight, height, chest girth, chest expansion, abdominal girth, posture measurements, and footprints.

Case No. I was overweight, short, large chested, with deficient expansion due in part to premature calcification of the costal cartilages, an excess of abdominal girth over chest of 1 inch (it should have been $2\frac{1}{2}$ inches less), a relative flat foot ($\frac{1}{2}$ inch in-curve on print), and a .34 posture. The author's index of posture is calculated on the deviations of the head forward, the back hollow and the protuberant belly from plumb lines touching the body in front and back. The height in inches (Ht) is divided by the sum of the deviations (Sd) multiplied by thirty. Good posture is 1 (unity).

$$\frac{\text{Ht}}{\text{Sd} \times 30} = 1 \qquad \frac{61.5}{(1\frac{1}{2}.2.2\frac{1}{2}) \times 30} = .34.$$

Bad posture reveals and causes poverty of health. Other measurements have their various meanings and uses for the clinician, and he is gradually becoming aware of it.

Physiologic Assay.—Every disease is essentially an exhibition of a special physiology put into play by the requirements of the occasion. We call it pathology. A cold in the head, a colitis, a surgical wound, or a broken bone, all require special functioning. This process supervenes upon the ordinary physiological affairs of living. Life must be carried on during the progress of the disease. Respiration, digestion, circulation, secretion, and excretion must continue. Blood repair and metabolism must be kept up and the autonomic system must manage it all.

All of these processes contribute directly to the antipathological fight to neutralize and dispose of toxic material. The whole body is engaged in every medical condition, from measles to myocarditis.

The demands may be severe, prolonged and urgent, and the outcome of the illness hang finally upon the condition and endurance of an organ or tissue not at all directly concerned. The heart does a laborer's work every day and night during the several weeks of a typhoid infection. Many other tissues are similarly employed. In fact, it is the failure of some of the sources of supply that is frequently the immediate cause of death. The ability and capacity of every organ is therefore of importance in any complete diagnosis and must form a large part of our synthetic process.

Therefore there should be recorded the results of tests of the function of the digestive system and its glands, the circulatory system, the kidneys, the endocrine glands, the autonomic and the cerebrospinal system at least. In this field, the tests for disordered function leading to disease diagnosis are well understood and commonly practiced. Their employment, however, may be overdone and the laboratory called upon to substitute for study and understanding. There is general scarcity of tests of the efficiency of ordinary functions.

In Case I the following physiologic data are selected:

Digestive system: Carmine, speed and clearance test. Speed twelve hours. Clearance forty-eight hours.
This indicates a normal speed but a delayed clearance, although "not constipated."

		Heart rate.	Systolic.	Diastolic.
Circulation:	Standing.....	120	104	60
	Horizontal.....	102	120	70
	Hemoglobin....	+18	−16	−10
	Index (author's).	+15	(75 to 100 is "normal")	

A rapid unstable heart, and with a weakened splanchnic tone.

Kidney: 1. Abbreviated report of catheter specimen:

Specific gravity,	1.006
Protein,	Marked trace
Casts,	None
Pus cells,	Numerous
Bacteria,	Numerous
Epithelial cells,	Many

2. Indigocarmine test: Right six minutes. Left four minutes, rapid normal.
3. Mosenthal: Good concentration.

Autonomic nervous system: 1. See Circulation Test.
2. Sergent test marked, but evanescent white line followed by red, pointing toward adrenal insufficiency.
3. Emotional instability.

Cerebration: 1. Complaints recited thirty minutes before stopped by examiner
2. Dramatizes complaints.

The weak points in the physiology of the patient appear definitely in the autonomic nervous system and in cerebration. She was conspicuously lacking in what is usually called "brains." Any process of cure and rehabilitation that might be initiated would be handicapped by these two functional inferiorities. And every prescription in the whole program should regard these weaknesses as well as the efficiency shown in other quarters. To one who has labored with this common condition, the counsel of despair on the part of a former physician when he gave the diagnosis "you are merely nervous," seems almost excusable.

There are reasons for every psychoneurosis (heredity, racial, social, economic, endocrine, etc.). A psychoneurotic patient, however, may be otherwise sick or well. She may or may not have a broken leg. She may or may not be suffering from a variety of ailments and handicaps which give substance to her complaints. If the removable handicaps are taken away there is some hope. If they are not taken away, there is no hope. The more progressive neurologists who are handling these cases are

more and more realizing the valuable aid that they can get from the internist, from the gynecologist, the nose and throat specialist, the pathologic and roentgenological laboratories, and the plain everyday, all-round general practitioner if he may be found. Stripping off removable handicaps leaves the psychoneurotic in a position where the best possibilities may be realized. If, in addition, weak physiologic processes are regulated and strengthened there is an even better prospect. So much for the pathology and physiology.

Environment, Regimen, and Conduct.—The next field is that of environment and reactions to it. It includes burdens, rest, recreation, relatives, habits, feelings, associations, hobbies, aversions, interests, hopes, fears, physical and psychological conditions, and circumstances of daily life generally. In this field may be included the important matters of diet and exercise.

In the present case, the woman was married to an indulgent husband who had not lived up to her expectations socially, financially, or sexually. She found her newly acquired relatives willing to listen to the recitation of her complaints which she would describe, elaborate, and dramatize. She would develop an incident in which she played the part of heroine with crude but high dramatic fervor which grew with practice. This encouraged her excellent powers of invention and her experiences became more real and fixed. Each one of her complaints was traceable to actual physical conditions. The disordered autonomic nervous system could be trusted to reproduce almost any symptoms suggested. As the various physical infirmities were whittled away, so the environmental elements which supported the psychoneurotic demonstrations were also mitigated. Diet was prescribed and motivated exercise taught and made interesting. Some simple, homely psychoanalysis was undertaken; some practical psychotherapy was put into operation. The therapeutic program was effectively supported and the purely personality field showed almost as highly satisfactory as the physical. The patient became active, interested in things which were outside of herself, commenced to lose weight, while her husband commenced to gain.

Conduct and environment form therefore the third group of elements in the assembly of a diagnosis.

History.—A worthily noted leader in an important field of medicine remarked in an unguarded moment, "Let me test the patient, I don't need any history." He would have missed the following selected data in heredity and history in Case I which would have helped him in caring for the woman. "The oldest child of Galician Jewish parents, one of whom died at forty-seven after a sickly life, the other alive at fifty-two, of a 'worrisome' disposition, a younger sister always tired. Measles, scarlet fever, and diphtheria in infancy, many colds on chest. Married four years, no children, precautions taken. Acute 'grippe' five times in six months. Severe dizzy spells, 'buzzing shocks,' weakness spells. Heavy pain on side of head. Appetite and sleep good."

These facts and many more carry their own significance without discussion. They present the kind and quality of the patient in bold outlines. The succeeding examination fills in the picture.

Thus the elements in the synthetic diagnosis are pathology, physiology, anatomy, environment and conduct, heredity, and history. When these are noted, recorded, analyzed, and their many mutual interrelations determined, the whole diagnosis can be synthesized and completed, and treatment of the patient may proceed at greatest advantage. Medical science has done its best, it can do no more, it should do no less.

Medical science is now going through a transition similar to that made in a parallel science. Two score years ago, we studied zoology and botany. We classified animals and plants into orders, genera, families, and species. We made a zoological diagnosis. Here was an elaps fulvus, there a sitta canadensis or an arctomys monax. We discovered new species, gloried in the achievement, and named them appropriately. There was an adolescent fervor akin to that in collecting postage stamps, the more rare and unusual, the better.

Now zoology and botany have outgrown the early collecting and descriptive phase which flourished from Herodotus to Lin-

naeus. They have become biology, a study of life processes, respiration, digestion, heredity, reproduction, environment, evolution. This is joining hands with the whole gamut of physical and social sciences, which are becoming synthesized into one.

So the older medicine isolated diseases, named, studied and collected them into books, as separate entities. The emphasis of the new medicine has changed from the disease to the man who is afflicted. It seeks to understand his reaction, to assemble his resources, to perfect his resistance, and to increase his capacities. The synthetic diagnosis is the practical expression of this unfolding of medical advance, not quite feasible for everyone, nor yet impossible to any—a way, a vision, and a goal.

Among the logical conclusions that seem to be close at hand, or at least within sight, are the following:

As practical steps forward, we might suggest that every specialist, obstetrician, and surgeon ask for a good survey with an assembled diagnosis with every "case" sent to him. Everyone sending a case to a specialist or surgeon should endeavor to furnish these data. Every case seen by a physician should get a thorough survey as soon as the emergency permits. Every patient admitted to a hospital should be given a complete survey on admission before operation, before discharge, before or after death, and the hospital that does this begins an epoch.

Every man of wisdom (or employed by such) will, in the future, have in his own hands or in the hands of his physician, a thorough health survey, including a synthesized diagnosis which may be used for reference in the event of illness by his future medical attendants. This should be continued through life, and be summarized and continued in his children's record. This will eventually create a body of fact that medical science has never yet seen. It will make possible rapid and enormous gains in disease management, and prevention and constructive medicine and eugenics. It is an essential in racial hygiene. To cooperate in this advance is one of the greatest privileges of the medical practitioner.

CLINIC OF DRS. LEWIS D. STEVENSON AND GEORGE H. HYSLOP

FROM THE NEUROLOGICAL SERVICE OF BELLEVUE HOSPITAL, FOSTER KENNEDY, M. D., DIRECTOR; AND THE DEPARTMENT OF PATHOLOGY OF BELLEVUE HOSPITAL, DOUGLAS SYMMERS, M. D., DIRECTOR.

PERITHELIOMA OF THE BRAIN: A CASE OF MULTIPLE PRIMARY PERITHELIOMATA; DISCUSSION OF HISTOPATHOLOGY

MULTIPLE primary tumors of the brain are unusual. It is safe to say that a correct clinical diagnosis is almost never made. Endothelioma of the dura and occasionally of the brain proper, glioma, are known to occur in multiple form. Perithelioma of the brain is ordinarily a slow-growing single tumor. In a series of 308 histologically identified brain tumors, Cushing and Bailey[1] found 5 cases of perithelioma.

Perithelioma may occur in various tissues of the body, especially in the adrenals and the carotid gland. It has been reported also as originating in the breast, the lung, the testis, in the medullary substance of the bone, and also in the subcutaneous tissues. However, there is some question as to the proper classification of many tumors which have been called perithelioma.

CLINICAL REPORT

The patient was a married man, aged forty. His personal history was negative except for the excessive use of alcohol until about a year before the onset of his final illness. In November, 1927 he fell against a boiler. He struck the back of his head and fell forward on his face. Aside from being shaken up a bit, there was no loss of consciousness and no evidence of skull or intracranial injury.

About two weeks later generalized headaches accompanied by nausea appeared. These symptoms continued through the winter and increased in

severity. In April, 1928 hoarseness and blurring of vision developed. By May the patient was unable to read due to progressively impaired vision. By June he had become completely blind, had a change of personality marked by apathy and forgetfulness, and was somnolent much of the time. Details of the course of the visual impairment or the presence of other symptoms could not be obtained from the patient or his wife, who had not observed any more than has been stated above.

The patient was admitted to the Neurological Service at Bellevue Hospital June 28, 1928. At that time examination showed no abnormalities except the following signs referable to intracranial disease:

Cranial Nerves.—There was advanced bilateral papilledema with retinal hemorrhages. The pupils were dilated and inactive to light, and there was complete blindness. There was a slight inconstant nystagmus on turning the eyes to the left. The left external rectus muscle showed partial paralysis and the left facial musculature was weak. The trigeminal nerves were normal. Swallowing and tongue movements were normal. At times phonation was impaired and the voice was hoarse. Vestibular function was not tested, but there was no deafness. The olfactory sensation could not be tested because of the patient's poor cooperation.

Motor System.—There was slight weakness of the left arm and leg on voluntary movement. When the patient attempted to stand he would fall backward and to the left. He could not walk. There was no ataxia in limb movements when recumbent, and succession movements were performed well.

Sensory System.—Except for what was judged to be a slight hyperesthesia on the left side of the body, there were no abnormalities.

Reflexes.—The patellar reflexes were absent. Other tendon reflexes were present, but varied from day to day. All the abdominal reflexes were diminished. The right plantar response was normal, but on the left there was a variable Babinski reaction.

Addenda.—Serology of the blood and spinal fluid was negative. The spinal fluid pressure was increased, but there were no cells and no increase of protein. Stereoscopic *x*-ray pictures of the skull were entirely negative and showed no evidence of increased intracranial pressure.

Although a left posterior fossa lesion was considered, the signs indicating pathology in this region were regarded as of false localizing value, and a clinical diagnosis of tumor of the right frontal lobe was made.

An exploratory craniotomy of the right frontal region was performed on July 6th. There was no tension of the dura, the surface of the brain was not unduly congested, and there was only slight flattening of the convolutions. No tumor was found, although the anterior half of the right hemisphere was explored.

Following operation, the clinical situation remained unchanged until August 4th, when the patient fell into a sudden coma and died within a few hours.

PATHOLOGIC REPORT

Complete necropsy was done. Careful examination revealed no gross pathologic changes except moderate sclerosis of the aorta and multiple tumor nodules in the brain.

The brain was the seat of multiple tumor nodules (Fig. 104) varying in size from a few millimeters to 3 cm. in diameter. In the left hemisphere there was a nodule 2 cm. in diameter in the frontal lobe about the middle of the second frontal convolution. There was a small nodule, ½ cm. in diameter, in the left occipital pole with one or two miliary nodules elsewhere. These masses were all subcortical. There was apparently some softening in

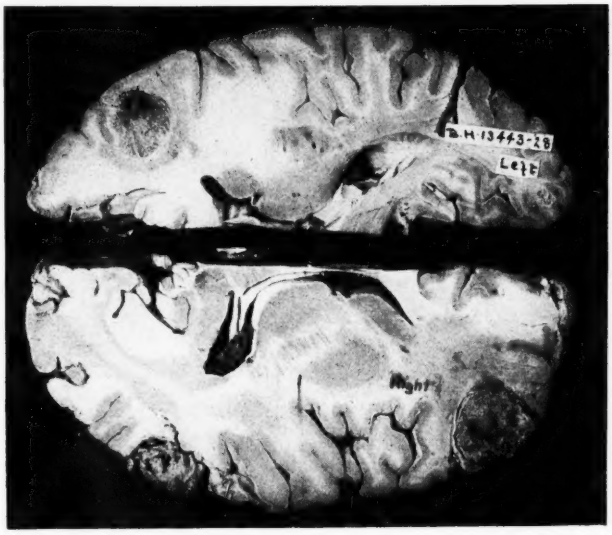

Fig. 104.—Photograph of brain showing tumor nodules (perithelioma) in both hemispheres.

the internal capsule and, to a slight extent, in the lenticular nucleus of the left side.

In the right hemisphere there were four large nodules, from 2½ to 3 cm. in diameter, and all appearing on the surface, one in the right frontal lobe involving the posterior end of the second and third frontal convolutions; another near the vertex about the top of the precentral gyrus; two in the right parietal lobe, one of them in the region of the supramarginal gyrus and the other low down in the junction of the parietal and occipital lobes. In this hemisphere also there were one or two miliary nodules. The ventricles were not dilated.

There was a nodule in the cerebellum, 1 cm. in diameter, in the middle line in the uvula of the vermis. There was no tumor nodule visible in the brain stem, the pons or medulla to explain the sixth and seventh nerve palsies, etc. The blindness was evidently due to secondary optic atrophy with very considerable proliferation of astrocytes in the optic nerves.

Sections were taken from nodules in both hemispheres and these showed the typical structure of a perithelioma or, as some authors call it, a perivascular sarcoma, the unit of the tumor being a rosette of elongated cells arranged about a thick-walled blood vessel (Figs. 105, 106). The tumor cells a short distance away from the vessels had become necrotic and these necrotic areas were filled with large, fat-granular corpuscles. The tumor cells seemed to

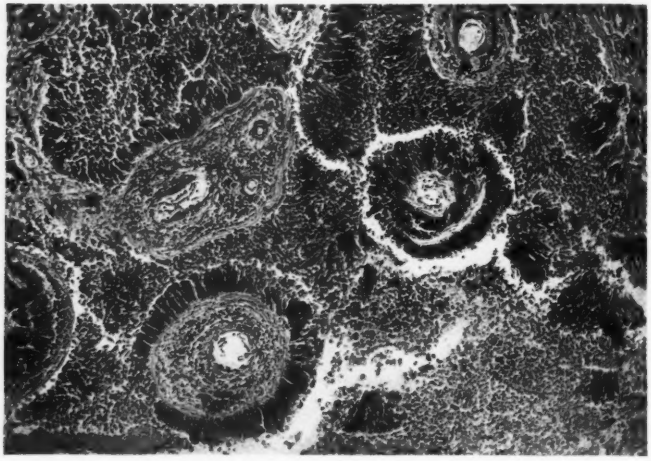

Fig. 105.—Photomicrograph showing general appearance of the tumor with numerous thick-walled blood vessels surrounded by radiating masses of tumor cells. Hematoxylin and eosin stain.

be growing away from the outer layers of the thickened blood vessels. In many regions the blood vessels had become so thickened that there was little or no lumen left. This resulted in complete disappearance of all the tumor cells near these occluded vessels. Some portions of the cortical tumors resembled angioma on section.

The tumor with which perithelioma is most likely to be confused histologically is the ependymal spongioblastoma (ependymoma). In the latter the cells are also arranged in rosettes, some of them about the blood vessels and some not

(Figs. 107, 108). In spongioblastomata of this type the delicate fibrils attached to the cells are readily demonstrable by Hortega's silver carbonate, and this alone would almost be sufficient to differentiate the two tumors (Figs. 109, 110). Again, the protoplasmic granules in the cells of these spongioblastomata are not present in the cells of the perithelioma. Another point of contrast is the peculiar tendency of the spongioblastoma to form ependymal surfaces, and there is no

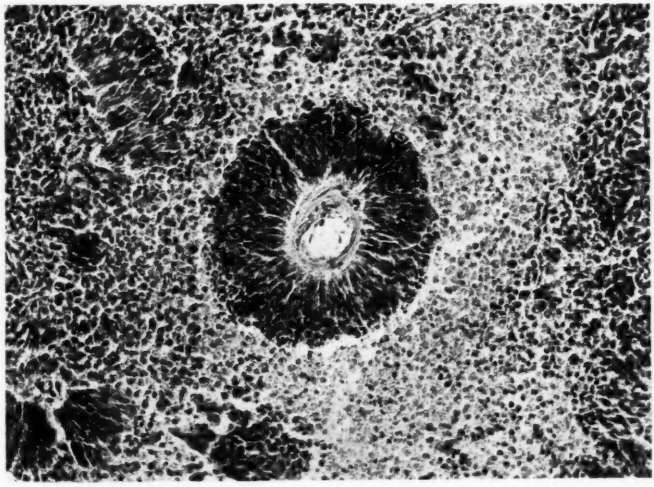

Fig. 106.—Photomicrograph showing the unit structure of the perithelioma surrounded by an area of necrotic tumor cells. Hematoxylin and eosin stain.

evidence of this in the perithelioma. Necrotic foci laden with Gitter cells are typical of the perithelioma and have not been present in our spongioblastomata to any such extent. In the rosettes of the spongioblastoma, the blood vessels are so loosely attached to the tumor cells that they frequently are seen to have dropped out of the secretion. This is not true of the tumor under discussion, where the tumor cells seem to be much more a part of the thickened wall of the blood vessel. There is, moreover, in the perithelioma a characteristic proliferative reaction

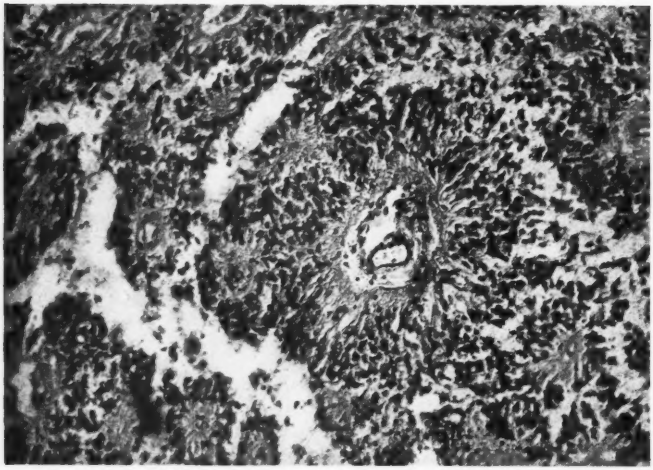

Fig. 107.—Photomicrograph of an ependymoma removed from the spinal cord, stained with hematoxylin and eosin, showing considerable resemblance to some peritheliomata.

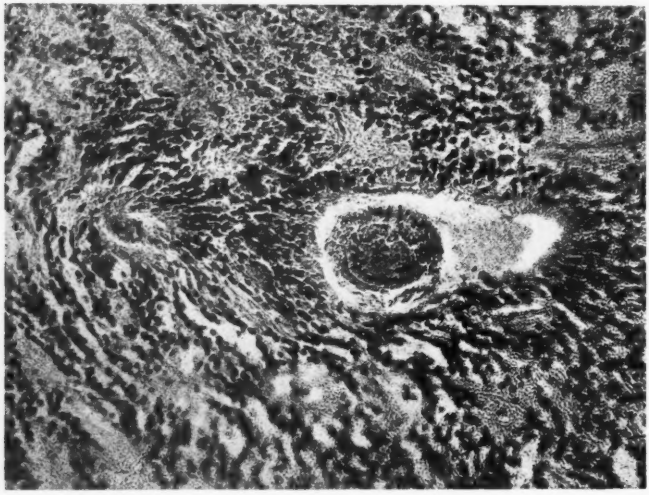

Fig. 108.—Photomicrograph of another ependymoma from the cervical region of a spinal cord, stained by hematoxylin and eosin.

in the vessels. As we have indicated, some parts of the perithelioma consist of nothing else but thickened blood vessels surrounded by areas of necrosis without any tumor cells left, and in many of these vessels the lumen has been entirely obliterated.

Concerning the term "perithelioma" and also the type of tumor described in this paper there is still a great deal of confusion. The descriptive name of perithelioma evidently arose from the belief of Eberth that there was a special type of cell

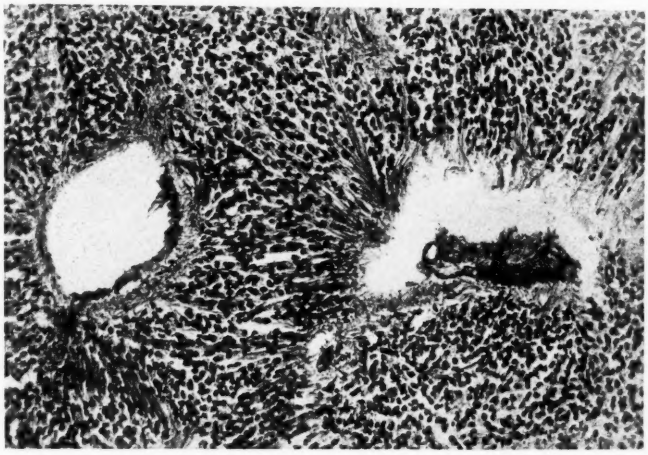

Fig. 109.—Photomicrograph of a section of the same tumor illustrated in Fig. 107, but stained by Hortega's silver carbonate method, demonstrating the neuroglia fibrils as well as the tumor cells radiating from a central blood vessel.

surrounding the blood vessels of the pia mater of the brain and that these cells sometimes gave rise to tumor formation. Similar cells, as Ewing[2] points out, have been described about the blood vessels of the hypophysis, carotid gland, adrenal, breast, salivary glands, and testis. Whether these cells have any special significance with regard to tumor formation in the brain is uncertain. It is certain, however, that pathologists in general are still confusing at least two quite distinct types of tumor of the

nervous system which they classify together as perithelioma. One of these is what might be called true perithelioma and is the subject of this paper, and the other is a spongioblastoma (ependymoma), which we illustrate in Figs. 107, 108. These two entirely different kinds of tumor look very much alike under the microscope when stained by the usual hematoxylin and eosin method. They can at once be differentiated by applying Hortega's silver carbonate solution to the frozen sections of material fixed in formol or, better

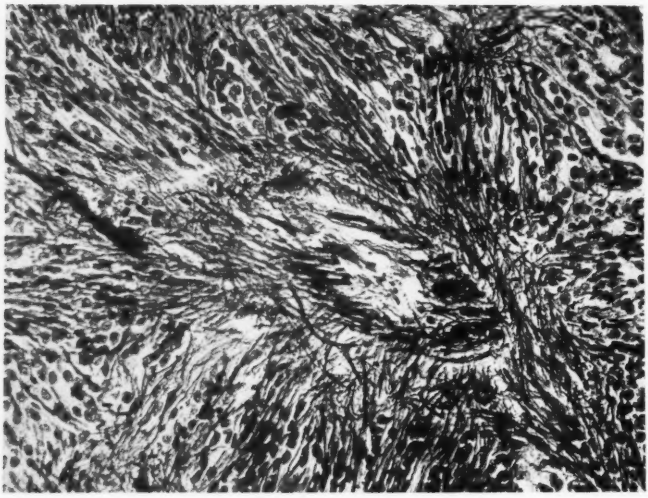

Fig. 110.—Photomicrograph of the same tumor illustrated in Fig. 109 stained by Hortega's silver carbonate, demonstrating the neuroglia fibrils in great profusion radiating to or from a central blood vessel.

still, formol-bromide. With the silver carbonate stain the spongioblastoma is seen to have great numbers of fine neuroglial fibers, whereas the perithelioma has none. Again, by the use of Van Gieson's stain, the thick-walled vessels of the perithelioma stain deep pink, whereas what appears to be a thick vessel wall in the spongioblastoma does not stain pink by Van Gieson's method, since it does not consist of ordinary connective tissue, but of neuroglial tissue.

Perithelioma of the brain is sometimes a metastatic tumor with the primary focus in some other organ (Fig. 111) which is from a metastatic nodule in the brain with the primary focus in the mediastinum. In the case presented in this paper, however, the tumor seemed to originate in the brain, since there was no evidence of any tumor formation in any of the other organs of the body.

The term "perivascular sarcoma" has been used to designate the type of tumor described in this paper. For example, Green-

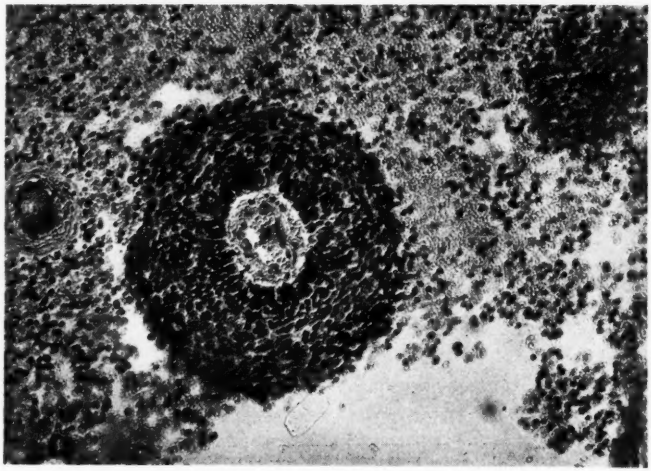

Fig. 111.—Photomicrograph of a perithelioma of the brain in Dr. Douglas Symmers' collection, where the primary growth was in the mediastinum with metastases to the brain and elsewhere.

field, in his paper published in "Brain" in April, 1919,[3] shows a photomicrograph of a tumor similar in some respects to our own (see his Fig. 8, Case XVI) which he calls a perivascular sarcoma; in his "Pathology of the Nervous System" he prefers this older term to the newer name of perithelioma. He believes, apparently, as we do, that these tumors may occur primarily in the brain and that they are usually single and rather slow-growing.

SUMMARY AND COMMENT

1. The case report is that of a man aged forty, who first suffered from headache and nausea, then developed visual impairment which in two months resulted in complete blindness, and within seven months after the onset of symptoms had mental deterioration, somnolence, and inability to stand or walk. Clinical examination led to a diagnosis of right frontal lobe tumor, which was not found at operation. Necropsy revealed the presence of multiple brain tumors which, on histologic examination, proved to be peritheliomata, and which were primary in the brain.

2. The early appearance of blindness cannot easily be explained; there was no internal hydrocephalus nor was there pressure on the chiasm, and we could not find tumor tissue in the secondary optic pathways. Secondary atrophy from advanced papilledema is the probable cause.

3. The onset of symptoms two weeks after a slight head injury may indicate that preexisting tumors were increased in activity. There is a mass of statistics bearing upon the causal relationship between injury and tumors. Ewing[2] quotes Adler, who found definite head injury to have preceded the onset of symptoms in 8.8 per cent of 1986 cases of glioma of the brain. It is well to call attention again to certain standards of evidence with respect to establishing the causal relationship between head injury and tumors of the brain. First, the injury must have been capable of producing some intracranial lesion, especially of the pia or dura, as well as of the brain substance in which the damaged tissue may eventually undergo neoplastic transformation. Second, it is important to prove the integrity of tissue prior to injury. Third, the onset of tumor symptoms should occur within a brief time—measured in weeks perhaps—after the injury. Applying these criteria to the case here reported, it can be seen that there is no true causal relationship between the slight head injury and the appearance of symptoms due to tumor. The effects of concussion on the pia mater might, in other instances, be of some significance where tumor of pial origin developed.

BIBLIOGRAPHY

1. Bailey and Cushing: Tumors of the Glioma Group, Lippincott, 1926, pp. 105, 106.
2. Ewing: Neoplastic Diseases, 3d ed., MacMillan, 1928, pp. 374, 424.
3. Greenfield: The Pathologic Examination of Forty Intracranial Neoplasms, Brain, vol. 42, Part 1, April, 1919, pp. 29–85.
4. Buzzard and Greenfield: Pathology of the Nervous System, Paul B. Hoeber, Inc., New York, 1925.

CLINIC OF DR. SAMUEL BROCK

UNIVERSITY AND BELLEVUE HOSPITAL MEDICAL COLLEGE

THE EPILEPSIES: I. THE NEURAL MECHANISMS. II. THE LESSER KNOWN TYPES

I THE NEURAL MECHANISMS

NEUROLOGY is indebted to the genius of Hughlings Jackson for the modern conception of the integrative mechanisms underlying central nervous activities. His noteworthy papers on the evolution and dissolution of the nervous system (1881–1887) as well as his numerous valuable publications on various phases of epilepsy (1861–1902), have given an inspired direction and impetus to work on this complicated problem. In fact, the further important contributions of Gowers, Sherrington, Ferrier, and S. A. K. Wilson in England, Muskens in Holland, Foerster in Germany, F. H. Pike and Rosett in this country—to name but a few of the host of workers—are largely amplifications and physiologic confirmations built upon the great foundation laid by Jackson.

Leaving aside consideration of the complicated pathophysiology involved in the convulsive attack, a matter I have analysed elsewhere,[1] the following question remains: What neural mechanisms underlie the extremely diversified epileptic symptom-complexes? Jackson frequently spoke of the "epileptic discharge." Many have stressed the "release" of one part of the brain by the removal of the *inhibition* exercised by higher elements in the neural hierarchy. Jackson believed that a redistribution of nervous energy could occur, viz., in the presence of a diseased pyramidal tract the energy normally transmitted by it could be shunted into other functionally related motor

pathways. The recent work of F. H. Pike and his co-workers,[2] to which further reference will be made, lends support to this viewpoint.

The Release Theory.—For Wilson[3] many of the phenomena of the major convulsive seizure are due to "transcortical decontrol," *i. e.*, the release of the "middle level" of Hughlings Jackson (*i. e.*, the motor rolandic cortex) from the inhibition exercised by the "highest level" (*i. e.*, the frontal lobes). The application of this principle applies as well to the sensory fit (including the uncinate type) as to the motor. However elusive and difficult of physiologic definition inhibition may be, it remains a potent factor in central neural function. In the seizures to be described, characterized by weakness and absence of movement (akinetic type), inhibition certainly plays a dominant rôle. It should be remembered that loss or diminution of consciousness, so common and important an element in almost all epileptic symptomatology, is a negative condition, an *inhibition* of function.

J. Rosett[4] has described a most attractive theory of the action of inhibition. His suggestion demands serious consideration for the understanding of the epileptic mosaic. He believes that in epilepsy "a wave of inhibition of nerve conduction proceeds in classic cases in an orderly manner along the several anatomic units of the sensory nerve pathways, from the receptors to the cerebrum and thence by the efferent pathways to the motor neurons of the lower neuraxis and so to the muscles." He points out that with the removal of function (by inhibition) of part of a neural pathway, the succeeding "nerve length" is released and exhibits excitation. Thus the wave of inhibition first strikes the "receptor-thalamic stretch," the thalamocortical is released and disorientation and simple hallucinations result (stage of aura). Next, the thalamocortical arc is engulfed by the inhibitory wave and cortico-cortical (association) pathways are "let go," further disorientation and composite hallucinations follow (viz., in the uncinate fit). As the association pathways succumb, complete unconsciousness appears and there is release of the efferent systems. The corticocerebellar is first activated and

muscular relaxation (stage of initial flaccidity) results. The function of the corticocerebellar pathway is "next extinguished and lower cerebellar and rubral (red nucleus) mechanisms are activated, resulting in muscular rigidity" (stage of tonic contraction). The pyramidal pathway next exhibits excitation and the stage of clonic convulsive movement is at hand. With the inhibition of the function of the pyramidal tract, one may elicit the toe sign of Babinski. This last speaks strongly for inhibition, because the Babinski sign is conceded by all to be indicative of defective pyramidal tract function. Lastly, as the lower cerebellar and the spinomuscular mechanisms are extinguished, general muscular flaccidity marks the end of the seizure. Recovery occurs in reverse order. Rosett points out that the inhibitory wave may stop anywhere along the above-described course and an incomplete seizure result. On the other hand, in their excellent monograph, Lennox and Cobb[5] wisely warn against a too schematic description of the motor and other elements comprising the convulsive attack. Any one conversant with the physiologic literature bearing upon this phase of the problem will readily agree with them.

A consideration of the many diverse types of the paroxysmal epileptic seizure, some kinetic, others akinetic, elevates the phenomena of neural inhibition to a position of importance. The suspension of function of such higher centers and pathways may well release lower units of the integrated neural apparatus and motor, sensory, psychic "releases" or "discharges" result.

The Short-circuit Theory.—This theory implies a special kind of "release." By reducing the number and complexity of the cerebral association systems certain lesions may prevent the normal delay and elaboration of impulses and cause a concentration of stimuli with a consequent explosive motor discharge. "The main difference between the release and short-circuit theories is that in release we think of removal or inhibition of a large functional unit of the central nervous system, whereas in the short-circuit conception any small or large portion of a nerve-conduction arc may be undermined and short-circuited. This theory would explain great variation in symptomatology . . ."

(Lennox and Cobb). It is not unlikely that just such "abnormally simplified arcs" (Southard) underlie the convulsive reactions seen so often in the feebleminded, whose brains lack the normal number of association fibers.

Closely related to short-circuiting is the theory advocated by Jackson, viz., the shunting and massing of nervous energy from a diseased pathway to a functionally related but healthy one. Such a concept is valuable in explaining some of the remarkable recoveries in cerebellar and vestibular lesions, which seem to depend upon the functional substitution of a destroyed part by an intact, similarly acting mechanism. Furthermore, as Pike points out, one need not fall back on the overworked hypothesis of inhibition and shock to explain the phenomena.

Applying this conception, Pike and his co-workers draw interesting deductions from absinthe-produced convulsions in cats with various lesions of the central nervous system. They believe that clonic convulsions arise from the cerebral motor cortex in the intact nervous system, but that they may arise (by way of this shunting of nervous energy) from lower motor mechanisms if the pyramidal tract is diseased. With Jackson, these investigators stress the unitary action of the motor mechanism, regarding it as quite improbable that one kind of convulsive movement should arise in one part of the motor apparatus, while another kind of convulsive movement arises in a different part, *in an intact nervous system.*

The Irritation Theory.—Others, notably Gowers,[6] believed that irritation plays the dominant rôle. All evidence pointing to the cortical origin of the convulsive movements partly favors the irritation theory.

Gowers stressed the fact that there was an association of movements in the convulsive state, not a mere addition of isolated muscular actions—a true observation pointing to a cortical origin. Indeed, Stenvers abroad and Rosett in this country have analysed convulsive movements by means of moving pictures, and have shown the patterned, integrated nature of the seemingly chaotic phenomena—observations which again indicate the cortical nature of the movements. Likewise, the absence of the

convulsions on the hemiplegic side in certain semiparalyzed epileptics, leads one to believe that the downward spread of the necessary corticospinal impulses is blocked by the lesion at the internal capsule. As stated before, however, Wilson believes that the motor cortex may be released from a higher prefrontal control, rather than be the site of irritation itself.

Certainly, focal and generalized convulsions can be elicited by electrical stimulation of the motor cortex. Foerster,[7] the distinguished German neurologist, is one of the main proponents of this theory, pointing out that positive signs of release do not necessarily follow immediately upon the sudden removal of inhibitory mechanisms. In most cases, an interval of time elapses in which there is diminished activity of the lower released centers also. Again the released centers do not exhibit their activity in an explosive manner. Furthermore, Foerster emphasizes the fact that the faradic current is a stimulant to the cortex.

The Explosive Theory.—If it is difficult to ascribe the chaotic phenomena of a fit to "any sequential blotting out of reflex levels" (Lennox and Cobb), is it possible that a general convulsogenic agent (such as a drug) or an abnormal metabolite can "set off" various cellular groups in the central nervous system simultaneously, resulting in a sudden widespread explosion? This is essentially a physicochemical conception, not a neural one. It may well be that the "release" or "irritation" mechanisms represent neural agencies which are used by the explosive factor.

In order to reach a working hypothesis one must agree with Pavlov's outstanding work,[8]—that excitation and inhibition are very closely interwoven cortical activities. Both sets of phenomena undoubtedly cooperate in the epileptic attack in varying proportions, depending upon the stage of the paroxysm and its type. Recent physicochemical studies lend weight to the "explosive theory." The type of the seizure will depend upon whether the detonation sets off excitatory or inhibitory mechanisms, or both.

II. THE LESSER KNOWN TYPES

The grand and petit mal are so well known that they need not be described in detail. However, study of the lesser known

types of epileptic reaction throws light on the question of the neural machinery involved in this disorder and for this reason these variants will be described briefly.

S. A. K. Wilson[3] divides them into motor, sensory, psychical, and visceral groups. The motor variants consist of (*a*) myoclonic (regional) epilepsy; (*b*) epilepsia partialis continua; (*c*) tonic epilepsy; (*d*) coordinated epilepsy, and (*e*) inhibitory (akinetic) epilepsy. The following descriptions are largely based on Wilson's contribution.

Myoclonic epilepsy consists of sudden "jumpy" twitches of various muscle groups, especially in the extremities, with no impairment of consciousness. They occur frequently as the patient is dropping off to sleep or early in the morning. The familial myoclonus epilepsy of Unverricht is a less common, but severer form associated with major seizures.

Epilepsia partialis continua (Koshewnikow) is a rare form of myoclonic twitching limited to a body segment. The irregular muscular contractions are almost continuous, and unassociated with exhaustion. The following case was studied in Bellevue Hospital on the Neurological Service of Dr. Foster Kennedy, to whom I am indebted for the privilege of reporting it.

Case I.—A young Jewess of twenty-two noted a peculiar involuntary twitching of the right thumb and index fingers at the age of eleven years. Three years later (at fourteen years of age) the "right side of the body" began to convulse at monthly intervals. Consciousness and urinary control were retained in the attacks, which lasted about fifteen minutes. She was not able to speak in the seizures; the facial muscles did not twitch. Vomiting and severe frontal headaches were apt to follow the paroxysm, but sleep did not.

Past History.—Birth was normal; no instrumental interferences were needed, yet the right upper extremity had been weak since birth. Defective vision has been attributed to a high degree of myopia. Except for scarlet fever at the age of six, no history of an infectious disease was elicited.

In May, 1929, the neural examination was as follows: The pupils were unequal and somewhat irregular; they reacted fairly well to light. The fundi showed changes indicative of a very high degree of myopia, but the retinal vessels were normal. There was a complete right-sided hemianopsia. The right lower face was somewhat weak. Speech was unimpaired. The right hand, more especially the thumb and index finger, showed more or less continuous twitchlike adductor movements which were quite irregular in ampli-

tude and tempo. These myoclonic movements derived an especial interest from the fact that this segment of the body was occasionally beset by outspoken jacksonian episodes. The right hand and upper extremity were often held in a rigid state resembling dystonia. At such times the posture of the hand reminded one of athetosis. It is important to note that the jacksonian episodes began in the right hand. This part was weaker than the left hand. The deep reflexes were equally exaggerated in the lower extremities; the right toes were not as flexor in response as the left. The deep reflexes of the right upper extremity were increased over those on the left. In the right hand position and joint sense, two point discrimination and deep pressure were defective. Astereognosis was present. Superficial touch, pain, and vibration seemed unaffected. There was a distinct psychic change; she was overemotional and facetious.

The lesion was believed to be in the left parietal lobe, extending rather deeply to involve the optic radiations and forward to implicate the postfrontal motor area. A cyst, residuum of a birth trauma, seemed likely. The only evidence of the lesion's progress was the increase in the number of Jacksonian seizures.

Operation (May 27, 1929) disclosed a large cavity in the left parietal region, from which about 40 cc. of a clear colorless fluid escaped. It undoubtedly communicated with the lateral ventricle, affording us an instance of true porencephaly. When the needle had been withdrawn, fluid continued to pulsate out through the opening in the dura, and through the tract in the thin, underlying layer of brain tissue. It was felt that atmospheric pressure must of necessity be forcing into the cyst a certain amount of air.

When there was no longer any appreciable escape of fluid, the muscle, fascia, and skin were sutured with interrupted black silk. The cavity was so large that it seemed unwise to remove any lining membrane

Tonic epilepsy relates to paroxysms of sustained hypertonus, usually involving the extensor, antigravity musculature. This is a human form of decerebrate rigidity, a "consequence of lesions dissociating physiologically, cerebral hemispheres from cerebello-mesencephalopontine levels" (S. A. K. Wilson).

Coordinated epilepsy is a phrase descriptive of attacks of patterned purposive movements. These automatisms are often seen during postepileptic confusional states. Rosett emphasizes the fact that coordinated movements may be discerned in many, even most, major convulsions when the latter are subjected to cinemato-analysis. In some patients, rotatory movements are exhibited, others in a running or pressing forward (epilepsia rotatoria and procursiva).

Inhibitory (Akinetic) Epilepsy.—That the epileptic discharge

can occasionally inhibit may come as a surprise to those who connote epilepsy with hyperkinesis. Yet a transient flaccidity precedes the tonic phase of the ordinary grand mal and may even constitute the entire attack—the static seizures of J. R. Hunt.[9] Again Gowers[10] stressed temporary motor weakness following sensory jacksonian seizures. In view of the question of excitation and inhibition just discussed, these cases are of especial interest in respect to the neural mechanisms involved in the major motor seizures.

In a carefully observed case of inhibitory epilepsy Wilson noted "defective inhibition of the antagonists" during the recovery from the stage of flaccid paresis. He refers this derangement of reciprocal innervation possibly to disturbed function of the cerebral cortex.

Inhibition is noted in our daily lives. Strong emotional excitation provides us precise, even dramatic evidence. One need only mention the weakness attending severe fright or associated with a bout of laughter.

The **sensory variants** are: (*a*) reflex epilepsy; (*b*) sensory epilepsy; (*c*) affective epilepsy. Reflex epilepsy relates to seizures following directly upon the reception of an extrinsic sensory stimulus. Foster Kennedy[11] narrates the remarkable instance of a little girl in whom a typical epileptic fit was always induced by flicking the nose. In another case, a sudden noise always caused a young epileptic boy to fall to the ground. As Wilson points out, here one sees inhibition of the brain stem's posture-maintaining mechanisms. In the cataplectic seizures seen in certain cases of narcolepsy, presently to be described, this form of inhibition will again be emphasized.

That a seizure may be purely *sensory* in nature need occasion no comment, especially in view of the phenomena seen in uncinate (temporal lobe) fits. Perhaps the most fascinating of the lesser known manifestations of epilepsy are these uncinate fits, originally described by Hughlings Jackson. They are largely sensory in nature and consist of a dreamy state associated with crude olfactory and gustatory hallucinations. Visual or auditory hallucinations may also be present. Since this symptom-com-

plex arises from abnormal activity of a diseased temporal lobe, with which visual field defects may occur, the visual hallucination may be projected into the blind visual field. Of especial interest is the recognition by the patient of the falsity of the visual hallucination during the fit.

The "dreamy state" has been analyzed by Wilson.[3] He divides it into (1) the familiarity or "déjà vu" type, in which the individual seems to be reliving a period in a kind of reverie; (2) the unreality type—a feeling of strangeness in an unfamiliar world; (3) the "panoramic memory" type—the reliving of a period of childhood, for example, a reminiscent reverie; (4) incomplete or abortive types. It would seem that we are dealing with complex phenomena conditioned by a decontrol or release of temporal lobe activities, brought about by inhibition of higher cortical areas—an act of transcortical inhibition with release (Wilson). Some years ago, Foster Kennedy made the illuminating suggestion that visual memories originating in early childhood or infancy were "stored" in the temporal lobe and that in disease of this part of the brain, they were "released" and revivified, as it were, in these peculiar hallucinations.

Now and again the inciting stimulus is of an affective (*i. e.*, emotional) type, the seizure following hard upon the exhibition of an emotional state.

To discuss in detail the psychic variants would lead us too far afield. Here we find mood changes, psychic equivalent, dazed and fugue states, ambulatory automatisms, deliria, furors, etc. Except the first named, all are associated with amnesia for the period of disturbance.

The **visceral variants** are of especial interest. Of first importance is the vasovagal attack of Gowers.[10] This is the result of "transient disturbance of function mainly in organs supplied by the pneumogastric nerve, . . . the patient complains of palpitation at the heart, difficulty in breathing, a suffocating feeling in the throat, hot flushes, icy coldness, sweating, shivering, and trembling, nausea," . . . a "creepy hollow or hungry" epigastric sensation, . . . a fear of impending catastrophe. These sensations are of periodic onset in those with or without

neuropathic antecedants (epilepsy, migraine, insanity, or neuroses in the forebears).

A recent unusual case, belonging to the category of the visceral variant type, may be briefly mentioned.

Case II.—A married woman of thirty-two has been suffering from the following seizures for six years. She suddenly is beset with a feeling "that blood is leaving her body," becomes weak and sits or lies down. Nausea follows, she belches up gas and her face turns pale. These seizures are unassociated with any impairment of consciousness; they appear in series of one to fifteen in a day with periods of remission of two or three months. As bearing upon the epileptic nature, it is to be noted that they not infrequently awaken her from sleep. They are invariably followed by severe frontal or occipital headache which does not occur apart from the attacks. These headaches have a definite migraine-like quality, and it is interesting to note that one maternal uncle was severely afflicted with hemicrania. These seizures may follow excessive fatigue or emotional upsets, but not infrequently come on without apparent cause.

The neural examination showed a visceroptotic, asthenic type of woman; the physical examination, an occasional irregularity of the heart beat.

Pyknolepsy.—In 1924 Adie[13] again called attention to a form of petit mal called pyknolepsy. He defined it as "a disease with an explosive onset between the ages of four and twelve years, of frequent short, very slight, monotonous, minor epileptiform seizures (six to one hundred daily) of uniform severity, which recur almost daily for weeks, months, or years, are uninfluenced by anti-epileptic remedies, do not impede normal mental and psychical development and ultimately cease spontaneously, never to return." These petit mal attacks have no characteristics by which one can differentiate them from those which precede grand mal attacks of the severer forms of epilepsy. Therefore, one cannot prognosticate in a given case of frequent petit mal attacks until a number of years have elapsed. Adie insists that all the elements of the definition be complied with, before a given case be admitted to this group and states further that "clonic movements, however slight, obvious vasomotor disturbances, palpitations, and lassitude or confusion after the attacks are equivocal symptoms strongly suggestive of oncoming grand epilepsy, and for the present they should be considered as foreign to the more favorable disease." Most observers regard this

peculiar syndrome as a disease sui generis. Hence its inclusion in the epileptic group may be questioned.

Narcolepsy.—In the past few years the subject of narcolepsy has again been brought to the fore, thanks to the recent studies of Lhermitte and Tournay[14] in France, and Adie[15] and Wilson[16] in England. Since its first description by Gélineau in 1880, these attacks of sleep or trancelike episodes have interested numerous observers.

Lhermitte and Tournay and Wilson divide the narcolepsies into the following categories:

A. 1. Traumatic.
   2. Psychopathologic (viz., hysteria).
   3. Toxic-infective (viz., epidemic encephalitis, lues, multiple sclerosis).
   4. Circulatory (viz., arteriosclerosis).
   5. Pressure (cerebral tumors especially in or near the third ventricle).
   6. Endocrine.
   7. Epileptic.

B. Idiopathic.

It is with the *idiopathic type* that most authors are concerned. In idiopathic narcolepsy the victim is beset by attacks of irresistible sleep or trancelike states, which come on without apparent cause. These may occur alone or in association with peculiar collapses in which the muscles relax suddenly—the jaw drops, the eyelids droop, the head lolls forward, the upper extremities fall limply to the side, the knees give way, and the individual sinks or slides to the ground. Though fully conscious, the patient is only able to articulate a meaningless sound. Grimacing, twitching of facial muscles, trembling movements, protrusion of the tongue, and stammering may also occur. The collapse may be complete or fragmentary, and is brought on by various emotions, especially pleasurable ones accompanied by laughter; occasionally anger is a precipitating cause. To this syndrome the term *cataplexia* has been applied by Adie,[15] who regards this "deposturing" as possibly the "clinical corresponding opposite of decerebrate rigidity."

It must be evident that we are dealing with a much exaggerated reaction having its normal prototype in the weakness accompanying strong emotions in normal man. The only neural examination of a patient in the cataplectic stage was made by Wilson, who found marked atonia, loss of the deep reflexes, and the Babinski toe reflex. With the return of motor power these findings disappeared. The patient was conscious throughout the attack.

Some of these patients experience causeless attacks of generalized powerlessness for which the name *catalepsy* has been used.

The English writers suggest that the collapse is brought about by inhibition of the brain-stem centers normally concerned in the maintenance of posture. They attribute the sleep attacks to the spread of inhibition through the cerebral cortex—a concept based on Pavlov's theory of sleep.[8]

Transitional variants between narcolepsy, cataplexia, and catalepsy occur, indicating a fundamental relationship or unity. For Wilson, the "periodic recurrence of attack, abrupt onset with or without aura, loss, or diminution of consciousness and the relatively brief duration" indicate an essential resemblance to epilepsy.

As a rule, the types of attacks occur independently; occasionally an attack on emotion ends in sleep. A feeling of intense weariness or headache may precede the attacks of sleepiness which number two to countless ones per day. The number is fairly constant for the individual.

He may have all the physical appearances of sleep yet be conscious and really in a state of "motionless awareness." On the other hand, the state may be one indistinguishable from normal, even deep sleep. Nocturnal sleep is always normal and its quantity bears no relationship to the number or intensity of these diurnal seizures. The latter are so compellingly inevitable as to take place under such conditions as walking, riding on a motor-cycle, during a meal, under bombardment, etc. The ensuing somnolence lasts from a few seconds to several hours, the average being several minutes. An external stimulus may pre-

vent the attack or very quickly rouse the victim. In one of Wilson's cases forcible attempts at keeping himself awake produced an attack of powerlessness. Anxious and vivid dreams have been described during the sleeping period. A few of the patients feel tired and sleepy between the actual seizures. The narcoleptic attacks nearly always appear first and may precede the other kinds by a year or more; occasionally the cataplectic seizures have preceded. In some cases the narcolepsy occurs alone over many years.

The idiopathic type of the disease begins oftenest in adolescence or early adult life, rarely later than forty. Males are much oftener the victims. Of about 50 cases, collected by Adie, only 2 were female. The individuals are healthy in all respects, except perhaps, for signs suggestive of pituitary disorder. The idiopathic variety lasts many years, is uninfluenced by therapy, and never manifests any hysterical phenomena. Occasionally epileptic seizures coexist.

In a previous review of this fascinating subject[17] reference was made to a remarkable case which I should like to describe briefly.

Case III.—E. is a single American-born man twenty-two years of age, whose family and past histories are irrelevant. In 1921, at the age of sixteen, he began to fall asleep in the classroom, while standing in the subway, and at other odd times. In the six and one half years since the onset he has had as many as eight narcoleptic seizures per day. The average is two or three per day, with a usual duration of minutes. The sleep may be interrupted in a few seconds. It has lasted twelve hours. The frequency of the attacks is not influenced by the amount of nocturnal sleep. At night he sleeps soundly. The seizures come on at any time of day. Under conditions conducive to sleep they are more apt to appear, yet he has fallen asleep while driving a motorcycle, an auto, and while eating, and occasionally while talking to people. Under the latter circumstance his conversation will drift from the subject to unrelated matters; this causes him considerable embarrassment. Upon external stimulation he awakens immediately and fully. If unable to sit or lie down, he walks about in a kind of "half asleep" state, remembering little of what occurs. He can do nothing to prevent the inevitable onset of the narcolepsy. Otherwise he is full of energy. He has been told that he often talks, laughs, and cries in his nocturnal sleep, and he believes that he has awakened himself by so doing. He has never walked in his sleep. He does not talk in the deeper narcoleptic seizures. Neither coffee nor alcohol have any effect on this pathologic sleep state.

The *cataplectic* or emotional collapses began in 1926 and are getting more numerous and intense. He first noticed it when he attempted to kill a fly with a "swatter." He had to grit his teeth and mobilize all his strength to overcome the weakness. Such abortive types of powerlessness have been described by others. Pleasurable anticipation (as meeting a friend), a prankish, "larky" feeling, and occasionally a hearty laugh cause his lower jaw to sag, his upper extremities to fall weakly by his side, his lids to close, and his knees to give way. He cannot talk at all. Most of these attacks are partial ones and he is able to brace himself without going "down in a heap." The fragmentary seizures occur once or twice a day. In January, 1928, a peculiar prankishness "came into his head" while walking in a hotel corridor. This time he collapsed completely, sank on his hands and knees, and struck and bruised his forehead on the floor. He is always completely conscious during these cataplectic states. On one cocasion anger precipitated a partial attack.

Cataleptic seizures began in the fall of 1923, while at college. It is a state of collapse or weakness coming on only *after* a narcoleptic seizure, particularly if he is recumbent and at home. It consists of an utter inability to move upon *awakening*. Powerless at first, he begins to "wiggle his fingers," then his hands, and then his feet; next he moves a foot and leg; then he stiffens his abdominal wall; finally summoning all his strength, he manages to sit up and almost always shakes his head about, as if to "clear it." If he tries too hard in his efforts to get up he gets dizzy. It takes him from five to fifteen minutes to get up when so seized. During the spell he talks in a mumble or not at all. This kind of attack has never followed normal nocturnal sleep or an emotional attack. It occurs two or three times a week.

Next, a remarkable hallucinatory episode may be mentioned. Occurring intermittently, it is limited to about one third of the aforementioned cataleptic seizures, arising under no other circumstances. While struggling to get up he sees a strange, empty room very clearly. Occasionally he sees either his brother or sister, or less often his mother, standing in the room or kneeling beside him. Everything is of normal size and contour. Most of the time they are silent. Occasionally the individual present gives him calm, gentle words of advice. Everything seems very real. Yet before he manages to get up *he invariably realizes that it is hallucinatory.* In fact, on a number of occasions he has managed to call some one in "to shake him out of it," and once his brother actually did! Although the details of the room may vary, the hallucination is almost always the same, and occurs only in the "twilight" state (Dämmerzustand) preceding complete wakefulness, during the peculiar powerlessness following a narcoleptic attack. There are no associated olfactory or gustatory phenomena.

Such hypnopompic hallucinations have been mentioned by the French authors, Lhermitte and Tournay, and in his second case Wilson records a comparable occurrence. In his patient the emotional content of a fearful dream precipitated attacks of powerlessness.

Twice in April, 1928, his vision became blurred during a cataplectic attack. He fell asleep both times after five or ten minutes. The cataplectic seizures had never been followed by narcoleptic episodes before.

His physical examination is entirely negative, except for a slight ptosis of the involuntary levator palpebrae on the left with a little enophthalmos (Horner's syndrome). Psychiatric examination discloses nothing of pathologic significance. He is an alert, cooperative, well-behaved, intelligent, well-oriented young man, with no abnormal trends. His memory is good. His emotional reactions (except for the "collapses" noted) are quite adequate. Insight and critique are normal. He betrays a normal concern over the manifestations described. His sex life has been one of complete abstinence, with a normal attraction for the opposite sex and a normal attitude toward his own. Study of his personality reveals a flighty superficial make-up leaning toward the cyclothymic.

All laboratory and *x*-ray studies revealed normal findings. The pineal gland was calcified.

Large amounts of pituitary and thyroid gland and caffeine were administered without relief.

In a recent contribution Levin[18] reports five new instances of morbid somnolence and cataplexy. He commends the use of the phrase, "Gélineau's syndrome" for cases presenting both of these symptoms. This author collected sixty-six typical case reports (including mine) from the literature, of which ten had an antecedent history of epidemic encephalitis.

BIBLIOGRAPHY

1. Brock, S.: Epilepsy and the Convulsive State, New York State Jour. Med., 1929, 29, 876.
2. Pike, F. H., Elsberg, C. A., McCulloch, W. S., and Rizzolo, A.: Some Observations on Experimentally-produced Convulsions. The Localization of the Motor Mechanisms from Which the Typical Clonic Movements of Epilepsy Arise, Amer. Jour. Psychiat., 1929, ix, 2, 259.
3. Wilson, S. A. K.: Modern Problems in Neurology, Wm. Wood & Co., New York, 1928.
4. Rosett, J.: The Epileptic Seizure: Its Relation to Normal Thought and Normal Action, Arch. of Neur. and Psych., 1929, xxi, 731.

5. Lennox, W. J., and Cobb, Stanley: Epilepsy, Medicine Monographs, Williams & Wilkins, Baltimore, Md., 1928.
6. Gowers, W. R.: Cited by Lennox and Cobb.
7. Foerster, O.: Cited by Lennox and Cobb.
8. Pavlov, I. P.: Conditioned Reflexes (transl. by G. V. Anrep), Oxford Univ. Press, 1927.
9. Hunt, J. R.: On the Occurrence of Static Seizures in Epilepsy, Arch. Neur. and Psych., 1922, 8, 315.
10. Gowers, W. R.: Epilepsy and Other Chronic Convulsive Diseases, London, 1901.
11. Kennedy, Foster: Epilepsy and the Convulsive State, Arch. Neur. and Psych., 1923, 9, 567.
12. Gowers, W. R.: The Borderland of Epilepsy, J. and A. Churchill, London, 1907.
13. Adie, W. J.: Pyknolepsy: A Form of Epilepsy, Occurring in Children, with a Good Prognosis, Brain, 47, 1924, 97.
14. Lhermitte, J., and Tournay, A.: Rapport sur le Sommeil Normal et Pathologique, Rev. Neurol., 1927, 1, 751.
15. Adie, W. J.: Idiopathic Narcolepsy, a Disease Sui Generis, Brain, 1926, 49, 257.
16. Wilson, S. A. K.: The Narcolepsies, Brain, 1928, 51, 63.
17. Brock, S.: Idiopathic Narcolepsy, Cataplexia and Catalepsy Associated with an Unusual Hallucination, Jour. Nerv. and Ment. Dis., 1928, 69, 583.
18. Levin, Max: Narcolepsy (Gélineau's Syndrome) and Other Varieties of Morbid Somnolence, Arch. Neur. and Psych., 1929, 22, 1172.

CLINIC OF DRS. MAURICE PACKARD AND H. F. WECHSLER

GOUVERNEUR HOSPITAL

EMBOLISM OF THE SYSTEMIC ARTERIES

EMBOLISM of the lesser circulation is unfortunately a common occurrence in a host of conditions. It is the surgeon's nemesis. In the absence of an active endocarditis, however, embolism in the systemic circulation is much rarer. We are fortunate to be able to show you today three examples of this condition in three women in this one ward.

Case I.—The first patient (A. S.) an American housewife, is thirty-five years of age. She has been complaining of precordial pain, shortness of breath and swelling of the feet and ankles, for the past six years.

Her family history is negative except for one brother who died of "heart disease" at the age of sixteen.

She had measles as a child and pneumonia in 1917 and again in 1923. Rheumatic fever and syphilis are denied by name and symptoms. Her menses began at thirteen and were perfectly regular up to a year ago, when irregular intervals of amenorrhea set in. Her last period occurred four months ago. She has been married six years and has had four miscarriages.

For the past six years she has been suffering with dyspnea and palpitations on exertion, moderate swelling of the feet and ankles and a dry cough. Intermittently, she has been subject to attacks of severe precordial pain, associated with marked palpitation, orthopnea, pain in the right upper quadrant and an increase in the edema of the ankles. Six weeks ago, following the removal of many abscessed teeth, she caught "cold" and had such an attack. She has been confined to her bed since that time. Her appetite has been poor and she has lost 20 pounds during this period. Three weeks ago, an abscess formed in the vulva, which however opened spontaneously. About ten days ago, she had a slight hemoptysis. Upon getting up out of bed, two days ago, she was suddenly seized with an excruciating pain in the right foot associated with a feeling of coldness and numbness in the affected part.

As you observe, she is very acutely ill. She is orthopneic and her respirations are labored, the alae nasae dilating with each inspiration. By the chart

her temperature is 104.4 F. and her respirations are 44. She is poorly nourished and developed, the visible mucous membranes are pale and the lips are cyanotic. No petechiae can be found.

The left pupil is slightly larger than the right but both react to light and accommodation, the media are clear and the fundi negative. The tongue is dry and furred and there is a foul odor to the breath. The pharynx is congested. The veins in the neck are engorged and pulsating. The thorax is symmetrical and of normal configuration. Both lungs are resonant to percussion throughout. Numerous moist râles can be heard over both bases posteriorly.

The apex beat can be seen in the fifth interspace and is very diffuse. By percussion we find the heart markedly enlarged, the right border being 6 cm. and the left in the fifth interspace 11 cm. from the M. S. L. A thrill is felt at the apex. The heart sounds are poor in quality, totally irregular and 142 in rate. No murmurs are audible. Her pulse is rapid, weak, irregular, and 120 in rate. A pulse deficit of 22 is therefore present. Her blood pressure is 120/74.

The liver is easily palpable four fingerbreadths below the costal margin and is tender. The spleen is barely palpable. The abdomen is apparently free of fluid. In the right labia majora is a small abscess from which pus is exuding.

Pretibial edema is slight, probably due to her prolonged rest in bed.

The right foot and leg up to the junction of the middle and upper third has a peculiar pale dusky hue. It is sharply demarcated and in comparison with the other extremity feels very cold. No pulse can be felt in the dorsalis pedis, posterior tibial and popliteal arteries. These can readily be made out on the left side. Although a pulsation is present in the common femoral artery, it is much weaker than that in the left. We will not trouble her by testing the sensibility of this area. That has been done and found to be completely lost. The right knee jerk is diminished.

A blood count taken yesterday gave the following: Hemoglobin, 60 per cent; red blood cells, 3,750,000; white blood cells, 9500; polymorphonuclears, 73 per cent. Her urine contains large amounts of albumin, a few granular casts, many white blood cells, and a few red blood cells. Her Wassermann is negative and her blood chemistry reveals a slight nitrogen retention, the non-protein nitrogen being 60 mg. and the creatinine 2.5 mg.

Case II.—The next patient (H. J.) has been under observation for a longer period of time. She is twenty-seven years of age, single, a seamstress, and was born in England. Her family history is essentially negative. Her past history reveals no previous illness except measles in childhood.

Six months ago she observed some shortness of breath on exertion, and had a slight cough. A physician whom she consulted told her that she had a "leaking valve." On the day of her admission to the hospital, while sitting in a chair reading a newspaper, she suddenly fell over unconscious. She was brought in with marked pulmonary edema, her eyes were deviated to the left, the normal creases of the face on the right side were absent, and a flaccid paralysis involving the right upper and lower extremities was present. The

abdominals were absent, and the deep reflexes on the right side were diminished. A Babinski could not be elicited. The fundi were negative. The heart sounds were barely audible due to the loud gurgling râles. The pulse was regular, of fair quality, rate 98. The blood pressure was 100/60. The liver and spleen were not enlarged and no edema was present. Her temperature was 102 F. A blood count taken immediately showed the following: Hemoglobin, 80 per cent; red blood cells, 4,400,000; white blood cells, 13,600; polymorphonuclears, 90 per cent.

That was her status on admission—you see her now ten days later. She is no longer comatose. However, a typical aphasia is now present. To all questions, although apparently comprehending them, she answers by one word "water." Her temperature and respirations are normal.

Examining her from a neurological standpoint, you notice that she is able to wrinkle her forehead yet her mouth is drawn sharply upward and to the right. Her tongue deviates to that side on protrusion. No ocular palsy is present. The media are clear and the fundi are negative. She is unable to move her right upper and lower extremities which are definitely spastic and show a beginning dropped wrist and ankle. The abdominals are absent and the deep reflexes on the right side are markedly exaggerated. A right-sided Babinski and ankle clonus are also present.

Her heart is not enlarged to percussion except in the second left interspace where the cardiac dulness is wider than normal. A loud presystolic crescendo murmur and thrill are now audible at the apex ending in a snapping first sound. The pulmonic second sound is accentuated. The pulses are equal, regular, rate 76, small and prolonged. The blood pressure is 88/55. The liver and spleen are not palpable, and there is no edema present. Various laboratory tests including urine, Wassermann, blood chemistry, and several blood cultures have yielded negative results.

Case III.—The third patient (A. E.) a housewife, forty-six years of age and born in Austria was admitted to the hospital complaining of swelling of the abdomen and loss of weight and strength.

Her family and marital histories are unimportant.

About nine months ago, she had difficulty in urinating and consulted a physician who told her she had an abdominal tumor. Three weeks later she was operated upon and a papillary cystadenocarcinoma of the ovary was removed. As peritoneal metastases were already present, several radium treatments to the abdomen were given after her convalescence from the operation. Her periods, which were regular up to the time, have been absent since these treatments.

During the past six months her abdomen has progressively enlarged and her difficulty in voiding has increased. She is now able to pass only very small amounts of urine at a time. For the relief of the abdominal swelling she was tapped at first at biweekly intervals and then about every eight days. She has had thirteen tappings in all.

Her appetite has been very poor and she has lost progressively in weight and strength. Her best weight was 190 pounds and is now about 100 pounds. She is also markedly constipated. For the past two months she has had

difficulty in breathing, an irritating cough and pronounced swelling of the feet and ankles.

A paracentesis was done yesterday and 6½ quarts of bloody fluid was removed. Twelve hours later, she complained of a sudden agonizing pain in the left hand and forearm and was unable to move the extremity.

She is now very acutely ill. Her temperature is subnormal being 96.8 F. She shows marked emaciation and her face has a pinched and anxious expression. The visible mucous membranes are very pale. Her eyeballs are slightly prominent, but there is no exophthalmos. The pupils are contracted due to the morphine administered. The thorax is symmetrical and shows no gross abnormalities.

There is limited expansion on the right side with flatness to percussion, absent breath sounds and diminished fremitus at the right base posteriorly below the angle of the scapula. Numerous moist râles are heard over the left base.

The apex beat is not visible but is palpable in fifth interspace 10.5 cm. from the M. S. L. A soft blowing systolic murmur is heard at the apex which is transmitted into the left axilla. The heart sounds are poor in quality and 116 in rate. Occasional premature contractions are present. The pulses are equal, poor in volume, 116 to the minute. The blood pressure is 100/60.

The abdomen is moderately distended, there is dulness in the flank and a fluid wave can be elicited. Above the pubis is a medial laparotomy scar about 6 inches in length. In the right hypochondrium and epigastrium is a hard irregular, tender mass 6 by 6 inches which moves slightly on respiration. The liver edge is blunt and palpable about two fingerbreadths below the costal arch. The spleen is not enlarged. There is marked edema over the sacrum and of the lower extremities.

The left hand and forearm up to 1 inch below the elbow joint has a blanched purplish color and the fingernails are blue. The skin is cold and has no sensation. The radial pulse is absent and that in the brachial is much diminished. The axillary and subclavian pulsations are normal.

A blood count reveals the following: Hemoglobin, 50 per cent; red blood cells, 3,000,000; white blood cells, 12,000; polymorphonuclears, 85 per cent. Her urine contains a small amount of albumin and many hyaline casts.

DISCUSSION

In the 3 cases which we have presented today, it is apparent that we are dealing with an embolism of a large systemic artery. It so happens that the embolus has come to rest in a different vessel in each patient and thus gives you an idea of the manifold possibilities that can occur in this condition.

Embolism of a blood clot naturally presupposes an initial formation of a thrombus in some part of the body. The knowledge of this connection we owe to the first work of Virchow, which

still remains a classic. The site of the thrombosis in our cases is in all probability the left heart: The auricle, ventricle, valves, or aorta. Emboli of the systemic circulation need not necessarily arise from the left heart exclusively. It has been shown by various experiments, especially by Teutschlaender, that small clots, bacteria, and such foreign particles as India ink granules can pass through the pulmonary into the systemic circulation. The size of the occluded vessels precludes such a possibility in our cases. There is, however, an avenue by which an embolus can avoid the pulmonary seive, namely, through an open foremen ovale, the so-called "paradoxical embolus." This is of such rare occurrence that it can be disregarded in our discussion.

The question as to the actual cause of the formation of thrombi is still in dispute. The older writers such as Eberth and Schimmelbusch and Welch assumed a primary injury to the endothelium, especially by bacteria. Aschoff and his co-workers however contend that the essential factor is a slowing or obstruction to the blood stream particularly if eddies are produced. Particles in such a stream will be deposited according to definite physical laws. The ball-valve thrombus occasionally found in the auricle has been advanced as a point against the necessity of endothelial injury. It has been shown, however, that if the auricles are carefully examined the site of its origin on some portion of the auricular wall can usually be found. In fact, cases have been described in which the thrombus was still attached by a thin pedicle, revealing the method of its subsequent detachment. Most pathologists today follow Ribbert in postulating two causes for thrombus formation—a slowing or irregularity in the blood stream—combined with a circumscribed, possibly microscopical, more or less damaged endothelium.

It is well known that due to its peculiarities in structure and the pathologic changes that so frequently attack it, heart thrombosis is very common. We need only call to your attention the auricular appendages and the intertrabecular spaces where the blood stream is normally reduced in velocity and the frequency with which various pathologic processes injure the endothelium of the heart and aorta, the common valvular deformities with

their consequent obstruction to the circulation and the stagnation produced by cardiac decompensation whatever its underlying cause.

Why a certain thrombus should become detached while the vast majority remain adherent at the site of formation is not entirely clear. A diminution in the force of cardiac contractility probably plays no rôle. The onset of such cardiac irregularities as fibrillation of the auricles or the return of the latter to normal rhythm under the influence of quinidine appears to have some etiologic significance. In any event, embolic episodes are frequent concomitants of these conditions. We know very little of the fermentative processes which could regularly cause a softening of the thrombus and its ultimate loosening.

The caliber of the artery occluded will depend upon the size of the embolus. Embolism of a large branch of the arch of the aorta such as the innominate, subclavian or common carotid arteries is very rare. Of the larger vessels, those most commonly involved are both carotids, the brachial, mesenterics, common iliac, femoral, and popliteal arteries. In the lower extremities, the left side is more commonly affected, probably due to the longer stretch from the abdominal aorta.

The results of such an occlusion will be determined by the size of the artery, its situation, the number of plugged branches, the energy or efficiency of the heart, and the number of available, dilatable collaterals. The usual consequence is, of course, an infarct in the organ supplied by that vessel, or gangrene of a variable portion of an extremity. Given, however, a favorable set of circumstances, such large vessels as the brachial, subclavian, or even the innominate can be occluded without any resultant gangrene. Konige has reported a case in which the left subclavian artery and its branches were completely blocked and yet produced only atrophy of the extremity. Bull in six thousand autopsies at Rik's Hospital, Oslo, found an embolism of the lower extremities fourteen times and once of the upper. In 7 of these 15 cases, gangrene was entirely absent.

The train of symptoms and signs following a sudden blockage of a large vessel to an extremity are practically pathognomonic.

The patient is seized with sudden agonizing pain in the affected extremity which is stabbing in character and requires large doses of morphine for its relief. In some cases of femoral embolism, the pain may be present at first in both legs and then later become confined to one extremity. This is due to the initial straddling of the bifurcation of the aorta by the embolus with partial obstruction of both common iliac arteries. In fact, the embolus can remain permanently in this situation. According to Key, prodromal pains may be present as a result of preliminary detachment of smaller emboli. Because of the devitalizing effect of the interrupted circulation on the tissues of the extremity, the pain usually gradually diminishes in intensity. Accompanying the pain, there is commonly a feeling of coldness, numbness, formication, or other paresthesias. Besides these local symptoms, there may be more or less collapse and prostration. The sudden increase in the peripheral resistance brought about by the obstruction to the blood flow in an extremity, acting upon a heart that is usually pathologically altered, may initiate the symptoms of cardiac decompensation such as dyspnea or aggravate them if already present.

The skin of the affected part assumes a peculiar, marble white, waxy, or ashen color and later becomes blotchy, mottled, and livid. It is sharply demarcated from the rest of the extremity. The temperature is markedly lowered, mobility and sensation are reduced, or entirely lost, and the deep tendon reflexes are absent. The normal pulsations of the arteries below the obstruction are no longer palpable. The localization of the embolus depends upon the accurate determination of this feature, as due to the collateral circulation, the height of the skin changes is not a good criterion of the level of the lesion. In thin persons, the actual site can often be felt as a thickened cord or merely as an increased resistance. The general signs are those of collapse and the evidences of the underlying cardiac disease, with or without decompensation. The temperature at first is usually subnormal and then becomes elevated. A leukocytosis of 10,000 to 15,000 and an increase in the polymorphonuclears to 80 to 90 per cent are usually present.

There are many conditions that can be confounded with this clinical picture and the differential diagnosis should offer little difficulty. In venous thrombosis, the pain is not as severe and is felt along the course of the veins, the extremity is warm, edematous, and cyanotic, the tendon reflexes, mobility, and sensations are intact, and the arterial pulsations are not impaired. Arteriosclerotic gangrene is characterized by previous intermittent claudication, its slow onset and progress and the direct evidences of vascular sclerosis. Gangrene due to thrombo-angiitis obliterans and Raynaud's disease can be distinguished by the history alone.

Within recent years great interest has been focused on the practicability of the surgical extraction of these emboli. Although as early as 1782, Lambert, an English physician, demonstrated on the horse the feasibility of arterial suture, his work lay dormant for over a hundred years. Interest was then revived by the reports of the successful suturing of veins by such men as Czerny and Schade. In 1896 Ssabanjeff made the first attempt to prevent gangrene of an extremity by the removal of the embolus. A host of workers, such as Murphy, Payr, Mattes, Carrell, and Garré then attacked the problems of arterial surgery both experimentally and clinically with the result that the procedure of embolectomy is now on a sound theoretical and practical basis. The first successful cases were reported by Mosny and Dumont and by Lahey in 1911 and there are now well over 150 cases in the literature in which embolectomy has been resorted to. These naturally do not include all the cases of embolectomy performed as many have probably not been recorded. Due to the zeal of Key, of Stockholm, by far the greatest number that have appeared come from Sweden. Less than 20 cases have been reported from the United States, Canada, and England.

Because of the secondary thrombosis that takes place below the occlusion, the outcome of surgical interference depends to a large extent upon early removal. The actual time required for this thrombosis to occur is variable. Lindberg found a secondary thrombus 86 cm. long as early as twelve hours, whereas Ipsen

could find no evidence of one two days after obstruction. In fact, Key has reported a successful extraction forty-eight hours after occlusion. The statistics compiled by the latter, however, demonstrate the importance of early removal. Good results were obtained in 45 per cent of those operated upon in the first ten hours, and in only 21 per cent in those between ten and fifteen hours. Between fifteen and forty-eight hours the percentage of successes remained practically stationary around 10 per cent. No benefit was noted in any case operated upon later than forty-eight hours after the onset of symptoms. The site of the occlusion is also of prognostic significance. In the same series, of those operated within the first ten hours, the proportion of successes was as follows: Axillary and brachial, three quarters; femoral, one half; iliac, one third; bifurcation of aorta, one seventh.

When the occluded vessel is quite small or an operation is contraindicated because of the general condition of the patient, the only measures that are of any usefulness are heat and vigorous massage. In cases belonging to the second category, ligation of the vein should also be considered. This increases the intracapillary pressure, and so tends to limit gangrene.

Before passing on the consideration of our cases, we wish to say a few words about embolism of the cerebral arteries. The vessels emptying into the circle of Willis supply different portions of the brain, but they so richly anastomose with one another that it is possible to inject the entire arterial tree through a single trunk. Provided the various branches are unaltered in structure and the occlusion is gradual, it is theoretically possible to have a complete obstruction of such a large vessel without serious consequences. Indeed, such cases have been reported. Unfortunately, a secondary thrombosis usually takes place which plugs the nutrient arteries. The highly differentiated nervous tissue is very susceptible to a decrease in its vascular supply and blocking the nutrient arteries will usually produce an area of necrosis and softening of brain tissue associated with a more or less pronounced edema. The focal symptoms will depend upon the size and situation of this area. As the middle

cerebral artery and its branches are the most commonly obstructed by an embolus, an hemiplegia is the usual consequence. The residual paralysis will depend upon the amount of actual necrosis.

ANALYSIS OF CASES

We are now ready for an analysis of our cases. The first case is classical. We have a young woman with a history of rheumatic fever and recurrent attacks of cardiac decompensation who was suddenly seized with severe pain and numbness in the right foot. Physical examination revealed evidences of mitral stenosis, auricular fibrillation, and cardiac decompensation, conditions which we have seen are common precursors of cardiac thrombosis and embolism. The right lower extremity to the junction of the middle and upper thirds of the leg exhibited a typical, early ischemia. Arterial pulsations were absent in all the vessels except the common femoral. However, they were much weaker than those on the opposite side. Marked prostration, fever, and a leukocytosis were also present. There is no question that we are dealing with an embolus occlusion of the femoral artery, probably at the origin of the profunda. The collateral circulation accounts for the limitation of the ischemia. Both because of her poor general condition and the fact that she was brought to the hospital more than forty-eight hours after the occurrence of the embolism, the surgeons who have seen her in consultation, have advised against operative interference.

The second case is also typical but of different situation. The patient is only twenty-seven years of age and has been complaining of but minor cardiac symptoms, when, like a bolt from the blue, she suffered a "stroke" with loss of consciousness and the later development of a complete right-sided hemiplegia including aphasia. Aside from the changes incident to the latter, her physical examination revealed nothing but a typical stenosis of the mitral orifice. Her blood pressure is not elevated, there is no evidence of arteriosclerosis, the eyegrounds are normal, and the urine and Wassermann are negative. The clinical picture can only be explained by an embolism of the left middle cerebral

artery. The flat temperature, the stationary heart signs and the repeated negative blood cultures exclude an active endocarditis. The embolus must therefore come in all probability from the left auricle. Why, in the absence of undue physical exertion, auricular fibrillation and cardiac decompensation, a thrombus should have formed and then broken loose from the left auricle of this young girl must remain unanswered.

The third case is similar to the first, but shows several interesting differences. She is the oldest of our patients, being forty-six years of age. She has been suffering for some time from a recurrent papillary cystadenocarcinoma of the ovary with peritoneal metastases which have necessitated frequent tappings and more lately with symptoms of cardiac decompensation. Twelve hours after paracentesis, she is suddenly seized with agonizing pains in the left hand and forearm. Physical examination, aside from the abdominal condition, revealed marked cardiac dilatation aud decompensation. The left hand and forearm showed the ischemia to have progressed to the stage of mottled lividity. No radial pulse was present, but a weak one could be palpated in the brachial. Collapse symptoms are pronounced, the temperature is subnormal and a leukocytosis is present. We are undoubtedly dealing with an embolic occlusion of the left brachial artery. There are no evidences of mitral stenosis or fibrillation of the auricles and the systolic murmur over the apex may be caused by a dilatation of the mitral ring. The cardiac lesion is in all probability a degenerative one. The embolus could conceivably be composed of tumor tissue, but the type of carcinoma she is afflicted with precludes such a possibility. Whether the paracentesis played any rôle in the detachment of a thrombus from the left heart, is questionable in view of the interval of time between the two occurrences. Surgical intervention has not been considered here, not only because of her extremely poor condition, but because of the nature of her major disease.

In conclusion, gentlemen, we wish to emphasize that, although embolic phenomena, according to Willius, occur in 25 per cent of those dying of cardiac disease, embolism of the ex-

tremities is fortunately uncommon; that when it does occur it is an exceedingly grave complication, and that modern surgery, early resorted to, offers relief in a large percentage of cases for a formerly hopeless condition.

CLINIC OF DR. ROLFE FLOYD

ROOSEVELT HOSPITAL

NEPHROSIS

THE case of a dropsical, pallid young woman forms the problem for diagnosis.

She has been swelling up for three weeks. She has no appetite and is weak, but complains of nothing else. She has no hypertension. He heart is normal in size, action, and sounds. Her eyegrounds are normal. Her urine is reduced in amount, about half a liter a day, with a gravity of 1.035 and boils solid. There are a moderate number of casts, mostly hyaline or finely granular, but no white or red cells. Her blood chemistry is normal except for a high cholesterol.

Several of those present are at once anxious to pronounce the case nephrosis because such cases of dropsy and albuminuria without hypertension or uremia are today unhesitatingly called "nephrosis," and are believed to be associated with some degenerative change or other in the tubular epithelium of the kidney.

I believe that such a use of the term and the idea that underlies it requires so many qualifications both through addition and exception that it is viciously misleading and tends to confuse the understanding of renal cases rather than to clarify it.

It is the purpose of this paper to show why this is so and how to avoid this unfortunate result.

GROWTH OF THE CONCEPTION

The term "nephrosis" was originally suggested by Friederich Müller at a meeting devoted to the kidney at Meran in 1905. After a pessimistic criticism of renal classification he suggested,

among other things, separating the definitely inflammatory lesions from those in which inflammation was absent or doubtful. For such predominantly degenerative lesions he proposed the name nephrosis.

Eight years later, 1913, Munk, in his work on Kidney Disease, followed this suggestion of separating degenerative renal lesions from inflammatory ones, but avoided the term "nephrosis."

A year later, 1914, Volhard and Fahr published their important work on Bright's disease and not only grouped all degenerative changes in the renal epithelium together under the term "nephrosis," but regarded such degeneration as the cause of renal dropsy, even when the dropsy occurred in the course of renal inflammation or nephritis.

The alluring simplicity of this view after so many years of confusion, together with the fine scholarship of Volhard and Fahr's work as a whole, resulted in the prompt and enthusiastic acceptance of this conception.

Volhard in a further exhaustive contribution in 1917 (included in Mohr and Staehelin's "System of Medicine") reiterates the same view practically without change. He however restates more clearly than before that the immediate cause of the dropsy lies in a disturbance of the function of the systemic capillaries and not in the kidney itself, but this vicious alteration in capillary function he believes to be caused in some unknown way by the lesion of the tubular epithelium.

Fahr, on the contrary, in his splendid article on the lesion of Bright's in Henke and Lubarsch's "Handbook of Pathologic Anatomy and Histology," published in 1925, completely retracts his former statement that ordinary degeneration of the tubular epithelium causes dropsy. He defines nephrosis as the degenerative lesions of the kidney which are caused by or incident to the fact that the kidney is a principal excretory organ. He further establishes the important fact that changes which he considers degenerative occur in the glomeruli in the chronic forms of nephrosis with which dropsy is associated.

Munk in the last edition of his book on Kidney Disease, also published in 1925, accepts the term "nephrosis" for all the degener-

ative lesions of the kidney and the various symptoms which are associated with them. He however assigns especial significance to the deposit of doubly refracting fat (cholesterin esters) in the renal epithelium. This constitutes "lipoid nephrosis" and is associated with dropsy, lipemia, massive albuminuria, high gravity and oliguria, without hypertension or uremia. He further insists that the condition is a general disturbance of protein and fat metabolism much more than a local kidney disease.

Epstein, who has studied the blood chemistry in these cases of massive dropsy and albuminuria, is also convinced that they represent a general metabolic disturbance rather than a local renal disease. Starling and his school similarly attribute such dropsies and albuminurias to alteration in the blood proteins rather than to a renal condition.[1]

So "nephrosis" is an attempt on the part of German workers to group all degenerative renal lesions and all the symptoms that occur with them under a single term.

Also it is recognized that two chronic types of degeneration, namely, lipoid and amyloid, are associated with dropsy and albuminuria and that just these same cases show changes in the glomeruli, which the "nephrosis" advocates consider noninflammatory.

Further there is a recent tendency to regard the dropsy and other symptoms in such cases as being caused by some general metabolic disturbance rather than by the lesion in the kidney.

So much for the constructive side of the concept.

THE LESIONS AND SYMPTOMS OF NEPHROSIS

It will now be useful to examine the lesions and the symptoms which occur in nephrosis as outlined by Fahr and by Munk in their contributions of 1925.

For nearly a century the term "degeneration" applied to the kidney has referred principally to changes in the epithelium lining the convoluted tubules, and the lesions of nephrosis are today described as involving principally these same cells.

[1] For a review of Epstein's and Starling's views on edema and albuminuria see Floyd's Kidney Disease, 1926, p. 131.

The changes in these cells are of two kinds, first, alterations in the normal components of the cells, and second, the accumulation in the cells of substances not normally present there, with more or less resulting perversion of cell structure and of cell function.

I. Alterations in the normal constituents of the cell.

(*a*) *Albuminous degeneration* consists in a precipitation of fine albuminous granules all through the cell body together with a decided swelling of the cells, probably by imbibition of water. It is not rare to find isolated red or pus cells in a tubule here and there. The Altmann granules of normal cells are disturbed in size and arrangement. Fahr, however, does not believe the albuminous granules are derived from them. This is the ordinary cloudy swelling and is caused by the toxins of most bacterial infections and by other poisons also. It is a very common lesion.

(*b*) *Droplet and Vacuole Formation.*—Instead of as infinitesimal granules, the albuminous constituents of the cell may be precipitated in the form of smaller and larger spherical bodies, which may attain half the size of the nucleus. They stain bright red with eosin. The albuminous and droplet forms of precipitate often occur simultaneously in the same cell. In addition to these precipitates, vacuoles may form in the cell bodies, but these are various in their content. They probably most often contain fat or some other extraneous substance and then belong to the group of changes to be described below, but they also may be formed of some of the original cell constituents in solution in imbibed water. In some cells with albuminous droplets and vacuoles the nuclei lose their staining power to a greater or lesser extent. There is good reason to regard the formation of larger albuminous droplets and of vacuoles as a later stage of albuminous degeneration induced by the same toxins through more concentrated or more prolonged action.

(*c*) *Necrosis.*—This lesion consists in extensive or wholesale necrosis of the tubular epithelium with coagulation, disintegration and desquamation of the cells. The nuclear staining power is lost. The glomeruli remain strikingly normal in contrast.

This lesion, which may be regarded as a final outcome of the process whose first step is albuminous degeneration, is caused by some metallic poisons and by a few infectious diseases, especially yellow fever and acute yellow atrophy of the liver. The most frequent cause is bichloride of mercury and this produces in addition to the necrosis, a deposition of lime in the dead epithelium and a growth of new epithelial cells to replace the old dead ones.

The symptoms of these lesions that alter the fundamental cell structure and do not alter the glomeruli have been recognized in this country, since Delafield described them nearly fifty years ago, under the name of "acute degeneration." The only symptom in the albuminous cases is the presence of a trace of albumin and a few casts, mostly granular, in the urine and even this is not constant. In the droplet and vacuole type there is a little more albumin (a heavy trace, not more), and a few more casts, but no other symptoms. Infrequent red and pus cells may not unusually be found in the urine by search. In the sublimate cases the amount of albumin is greater and there are many casts and much detritus. Pus and red cells are not hard to find, but by no means a feature. In addition there is oliguria and often complete suppression. If the anuria persists the nitrogen waste collects in the body, but seldom reaches alarming figures, seldom over 150 mg. of nonprotein nitrogen, and has never been the cause of death in any investigated case that I have seen. Dropsy and hypertension are so extremely rare that they are not to be considered as belonging to the condition. Eyeground changes are absent.

So in this first group of cases where alteration in the normal constituents of the cell occurs the kidney lesion is produced by a recognized cause, generally a toxin or metallic poison. It comes with the entrance of the poison into the blood and disappears when the poison is no longer active. In other words, it is a secondary lesion. Because of its excretory function and the consequent concentration of the poisons in it, the kidney is apt to show more damage than the other organs in which no such concentration occurs. It is a notable fact that these lesions, while causing similar changes in the urine to those seen in frank

inflammatory lesions (nephritis), do not cause dropsy, dyspnea, hypertension or eyeground changes. Even when so extreme that wholesale death of the epithelium of the convoluted tubules results, they still do not cause such renal symptoms, and only cause uremia through suppression of urine.

The albumin and the casts may be in part derived from the epithelial cells but certainly come in part from the blood stream, as do the infrequent red and white cells, and therefore constitute an exudate.

II. The accumulation of abnormal substances in the cells with resulting damage to function or structure.

(*a*) *Fatty Degeneration.*—The occurrence of neutral singly refractive fat in the renal epithelial cells has been recently exhaustively studied and while entire unanimity of opinion about the reasons for its occurrence has not yet been reached, certain ideas are generally accepted.

It is a very frequent event and small amounts of fat occur in some normal kidneys.

If present in considerable amount it is believed to mean a deteriorated or disturbed cell function.

Many observers think the most usual reason for it is that the cell fails in its ability to assimilate fat, but that the fat supply or intake continues, resulting in an excess.

It may occur when the blood fat is excessive, as in lipemic diabetes. It also appears in dying cells, as a product of disintegrating protoplasm.

Altogether the occurrence of neutral fat is probably the most frequent alteration from normal that occurs in renal epithelium. It is not only very often associated with all the forms of degeneration here described, but with all kinds of nephritis as well.

In droplet degeneration it contributes to form some of the vacuoles seen in such cases. It is more likely to appear in degenerations of longer standing rather than in those of short duration.

Clinically it causes no symptoms except the occurrence of neutral fat in the urine and in the casts. It is uncertain if it may alone cause a trace of albumin and a few casts.

(*b*) *Accumulation of various substances other than fat in the tubular epithelium which may, if excessive, damage the cell structure and cell function.*

Glycogen may accumulate in the cells of Henle's loop in diabetes to such an extent as to deform the cells.

Uric acid or lime may be deposited in renal epithelium in gout and other conditions with damage to the cells involved, but not on such an extensive scale as to damage the kidney as a whole.

Hemoglobin and other blood pigments may appear in the renal cells in cases of blood destruction in sufficient amounts to distort and severely damage the cells.

Bile also may load the tubular epithelium and be associated with albuminous degeneration, albumin in the urine, and bile-stained granular casts.

None of these substances in the kidney cells ever lead to dropsy, dyspnea, hypertension, eyeground changes, or any other renal symptoms except the albumin and casts in the urine already noted.

There are two more renal lesions included in the nephrosis group, namely, *lipoid degeneration* and the *amyloid or waxy kidney*. Here lies a main cause of confusion in the nephrosis question for it is here that the loss of distinction between nephrosis and nephritis occurs and clear definitions become impossible. There are two reasons for this: First, the symptoms that occur with these lesions include massive albuminuria, dropsy, and sometimes uremia; and second, the lesions are not strictly confined to the tubular epithelium, as in all the lesions already described, but involve to a greater or lesser extent the glomeruli, the blood vessels, and the stroma as well. So, whatever the name, it is obvious that here we are dealing with a group whose lesions and whose symptoms are much more allied to those of nephritis than to those of the types of degeneration so far considered.

It is necessary now to digress for a moment to define nephritis, so as to understand just how closely lipoid nephrosis and the waxy kidney are related to it.

Definition of Nephritis.—This term means an inflammation

of the kidney, a defense reaction in response to some injurious agent, a reaction which it is quite generally believed must be expressed in part at least by an exudation of the cells of the blood and of some of its fluid constituents through the walls of the capillaries into the inflamed tissue and into the urine. Another expression of inflammation and an important one in the kidney, is proliferation of either epithelial or connective tissue cells.

An acute nephritis therefore can consist of an exudate alone, but there is almost invariably some proliferation as well, a proliferation namely of the cells of the glomerular tufts. There may be a similar multiplication of the cells lining the capsule of Bowman. In some cases of acute nephritis there is also a rapid growth and reproduction of the connective tissue cells of the supporting stroma from the very first days of the disease. Some of the degenerative changes in the tubular epithelium described under nephrosis regularly form part of the lesion.

As acute cases pass over into chronic ones an increase of the connective tissue stroma becomes an almost inevitable part of the lesion, so much so that some observers have made stroma increase a criterion of chronic nephritis.

Another change that occurs as the lesion grows older and which is almost but not quite as inevitable as the stroma increase is a sclerosis of the arterial branches.

The symptoms that occur when the kidneys are inflamed are albumin and casts in the urine and blood cells in acute or exacerbated conditions, dropsy, hypertension, and its results, eyeground changes, uremia.

Hypertension has been thought by some authors to be a constant feature of nephritis, but this is unquestionably an error. While it is the rule there are exceptions.

(*c*) *Lipoid Degeneration.*—This consists in the accumulation of doubly refractive fat (mostly a cholestrin ester and related substances), in the epithelial cells and sometimes in the interstitial tissue. Droplet and fatty (singly refractive glycerin ester) degeneration, as above described, may also be present. The lipoid filled cells are swollen and their nuclei may lose staining power and the cells may desquamate.

The glomeruli often show thickening of the walls of the vascular loops with more or less hyaline substance deposited in them, there may be slight localized increases in the tuft cells, adhesions between tuft and capsule may occur, and finally shrinkage and atrophy may take place.

The intertubular stroma not only contains lipoid and some swollen lipoid-filled cells, but also shows definite streaky increase of the connective tissue cells and fibers.

The collection of lipoid in the renal cells was regarded by Kaiserling, who described it, as a much more definite evidence of a deterioration of the cell life than is the case with ordinary fat. Munk, who has devoted much study to this condition, holds to this view, but he thinks the physical form of the lipoid deposits within the cells may interfere with the cell life more than the more soluble singly refractive fat.

This lesion is of slow development and long standing so the tubular cells are found in different stages of deterioration and regenerating cells have been described by Fahr.

It is believed by observers who favor the nephrosis idea that the lesion may go on to cause a typical nephrotic atrophy of the kidney.

The cause of the condition is unknown. It is not caused by the toxins of the ordinary infectious diseases, nor by the metal poisons. Some cases are believed by both Volhard and Munk to be due to syphilis.

The symptoms usually associated with this lesion are those described at the beginning of this paper and it is not necessary to again rehearse them.

The lipemia and the disturbance of water balance through extrarenal factors together with the successful treatment of some cases with thyroid extract have led Munk and also Epstein to regard the condition as a general metabolic one, rather than one directly caused by the renal lesion.

It is most important to understand how *rare* such cases of pure lipoid nephrosis are for here lies hidden much of the mystery and confusion that shrouds the term "nephrosis." Lipoid nephrosis, like a ghost, is talked of by all, though seen by a very few.

Fahr writes: "Cases of pure (lipoid) nephrosis, such as those above reported, seem in general to be very rare, *less so at the bedside, than at the autopsy table*. While the number reported of clinical cases increases slowly and the clinical picture grows steadily more familiar to the clinician, the number of cases established beyond doubt by histologic study is still extremely meagre." Many men of experience have never seen a proven case. Personally, like others, I have seen cases with the clinical picture but without autopsy. The only typical case I have had a chance to follow to autopsy in recent years proved to have nephritis. Moreover many observers have reported cases which began with the typical clinical picture of nephrosis and after the lapse of months or years hypertension, cardiac hypertrophy, eyeground changes, and uremia developed, and the clinical picture of chronic nephritis then supervened. I have seen several such cases.

Long before the "nephrosis question" existed kidney cases with large amounts of dropsy and albumin, but with little or no hypertension or cardiac hypertrophy were generally recognized. They were usually called "chronic parenchymatous nephritis." Delafield called them "chronic nephritis with exudation." These cases have not ceased to occur just as often as they did before the term "nephrosis" was coined. An overwhelming majority of them, when they come to autopsy show the lesions of nephritis and not of nephrosis. As a great rarity one comes along that shows lipoid in the tubular epithelium with little pathology in the glomeruli, stroma or blood vessels. These rare curiosities are the only ones in the entire nephrosis group, except for the waxy kidney to be presently discussed, that suffer from dropsy, but in reading and talking about nephrosis the countless numbers of kidneys with albuminous, droplet, and fatty changes, together with the not unusual necroses from the metal poisons are all forgotten and the term "nephrosis" has become inextricably linked at the bedside with the idea of dropsy. Yet the vast majority of those who use "nephrosis" with this connotation have never seen a case of dropsy associated with a degeneration of the tubular epithelium alone.

(*d*) *Amyloid Degeneration or the Waxy Kidney.*—This lesion is characterized by the deposit of amyloid substance in the walls of the glomerular loops and of the small arteries of the cortex. In addition there is regularly more or less droplet, fatty, or lipoid degeneration of the tubular epithelium. Increase of connective tissue stroma develops as time passes and may reach an extreme degree, with consequent compression and destruction of the secretory elements. The arterial branches often show sclerosis, though this change may not be present in early lesions.

The glomerular lesion may result in serious narrowing or occlusion of the vascular loops, in a multiplication of the tuft cells which is usually limited in amount and localized to a part of a glomerulus and of a very uneven development in different glomeruli. As time passes more and more of the glomeruli change into almost structureless balls of hyaline connective tissue. The tubes, especially in the later stages of renal atrophy, may be dilated and have very flat epithelium and may contain very numerous casts and some blood cells.

Amyloid is a protein derivative and appears in many other organs besides the kidney. It is closely related to hyaline substance into which it changes with time as shown by special staining, but all hyaline does not by any means start as amyloid.

Amyloid appears in the various organs chiefly as the result of long-standing tuberculosis or prolonged suppuration, especially in bones. Its genesis is not understood nor why it is deposited almost exclusive in the vascular walls.

The amount of amyloid in the kidney varies a great deal. Often only an occasional glomerulus will show a little of it in one or two loops, and the kidney may be otherwise normal. From this minimal lesion all gradations occur up to the fully developed lesion, just described, in which every glomerulus shows extensive changes.

Symptoms are totally absent in the minimal lesions, but as the lesion advances the clinical picture becomes that already described for lipoid nephrosis. Except that it is my understanding and experience that the urine volume is apt to be more copious, its gravity lower, and lipemia much less pronounced or

absent. The dropsy does not develop in any exact proportion to the amyloid deposits in the kidney. When the kidney atrophies uremia develops and some hypertension is also likely to occur.

The amyloid kidney was described in 1842 by Rokitansky. The practically constant association of its lesions with its symptoms had made it one of the best defined and most generally recognized groups of Bright's disease till Volhard and Fahr included it in their nephrosis group in 1914. They stated that its lesions were not inflammatory, that the amyloid deposit was an incident, that its essential pathology was the degeneration of the tubular epithelium and that the latter lesion caused the associated dropsy.

Fahr, writing in 1925, retracts the statement that the ordinary epithelial changes cause the dropsy. He is also unable to find that the amount of lipoid in the epithelium varies in proportion to the development of the rest of the lesion. He still holds, as does Munk, to keeping the waxy kidney in the nephrosis group because the increase in the tuft cells in the glomeruli, while considerable and frequent, is by no means as great or as general as that seen in nephritis.

The advocates of nephrosis now take another step and it seems to me a totally unwarranted one.

Basing their statement on the pure lipoid nephrosis cases which they admit occur perhaps once in several hundred thousand instances of nephrosis, as they themselves have defined it, they say that when renal dropsy and much albumin in the urine are prominent features in nephritis, this is due to a "nephrotic component" ("nephrotische Einschlag"). This is surely a vicious use of terms because neither albuminous, droplet, necrotic, fatty, or vacuolar degeneration nor the presence of bile, glycogen, hemoglobin, or foreign dyestuffs in the renal epithelium have anything to do with dropsy or massive albuminuria. The genesis of dropsy is not well understood. It is generally regarded as being due to disturbed function of the capillaries. In nephritis it is hard to know what part the heart and what part the kidneys play in its production. Many good observers believe the composition of the blood a major factor. Further, a retention

of sodium chloride is believed, especially by the French school, to be most important.

Fahr has studied the relation between dropsy during life and lipoid in the renal epithelium after death. He believes there is some relation between them not only in lipoid nephrosis but in waxy kidneys and in chronic nephritis as well. It is a most interesting observation. I do not understand that he has yet studied the relation between lipoid and the amount of albumin in the urine.

Pending the confirmation and extension of this observation of Fahr's by others there is no objection to considering the possibility of the presence of lipoid in the renal epithelium in cases with much dropsy and albumin and even to speaking of a possible "lipoid" element in such cases so long as we remember there are many other more probable causes. This is very different, however, from fastening the connotation dropsy to the term "nephrosis."

No catalog of the lesions and symptoms of nephrosis is complete without a mention of the eclamptic kidney. This is a very obscure subject but the idea is steadily gaining that the renal lesions of eclampsia are due to a toxin not of renal origin circulating in the blood and are therefore to be regarded as degenerative and secondary. Further it is not believed that failure of renal function causes or contributes in any important way to the symptoms that occur. On this basis the eclamptic kidney has been tentatively included in the nephrosis group.

CRITICISMS OF "NEPHROSIS"

In Germany Aschoff and his school are bitterly opposed to the introduction of this term. Their attack is levelled not at details and subgroups, but at the basic conception on which the group is founded, namely, at the conception of degeneration. Inflammation is now briefly defined as a defense reaction. Most German pathologists regard the changes in the renal epithelium here discussed as degenerative from the start, in other words, as damage done to the cells which produce vicious alterations in their structure and function. Aschoff says, on the other hand, there is

no sanction for denying to the individual cell the capacity of a defense reaction. While the stage of increased vigor is extremely fugacious and impossible to demonstrate, he believes that it invariably precedes the stage of deterioration. He therefore considers all the described changes in the renal epithelium as inflammatory in character and the conception of cellular lesions degenerative from the start a fundamental error. This is a well taken and very interesting point, but it can hardly disturb the fact that in the kidney some lesions concern chiefly the tubular epithelium, others chiefly the glomeruli, others which are characterized chiefly by exudation of the contents of the blood vessels, others by growth of interstitial connective tissue, and still others by sclerosis of the vessels, and that the various lesions are associated each with somewhat different effects.

I have two objections to "nephrosis" as at present defined. First, it includes too much, and second, the peculiar characteristics of one subgroup, numerically infinitesimal in proportion to the rest, dominates and colors the conception of the group as a whole, making dropsy and nephrosis almost synonymous.

Albuminous, droplet, and vacuolar conditions of the tubular epithelium together with accumulation in it of neutral fat, glycogen, bile, hemoglobin, dyes, etc., all occur without the association of any change in the glomeruli or stroma. With these lesions no renal symptoms, but a trace of albumin and a few casts ever occur and often not these, so exudation is not constant and unimportant. Even with wholesale necrosis of the epithelium there are no glomerular or stromal lesions. There is, however, more exudation which includes some cellular elements, but no other symptoms of nephritis except when uremia develops incident to suppression of the urine.

All these cases may properly be grouped together from both the standpoint of change in structure and that of change in function.

Such changes in the renal epithelium occur not only alone, as here described, but also form a regular component of nephritis where their exact clinical significance is still obscure. In this sense nearly every case of Bright's has a "nephrotic component,"

but this is not at all what the special pleaders mean, for these epithelial lesions have nothing to do with dropsy.

Sharply distinct from all these conditions stand the last two groups, lipoid nephrosis and the waxy kidney. Here there are changes in the glomeruli and stroma, often pronounced ones, and clinically, dropsy and decided albuminuria.

It is hazardous to generalize about lipoid nephrosis, a disease of which there are only a dozen or so of established cases, but the waxy kidney shows very close affinities to chronic nephritis and not infrequently develops hypertension, eyeground changes, and uremia as time passes.

The waxy kidney has been a well-defined group of rena disease for three generations and I can see no reason for not letting it continue for the present to be so. As for saying that the amyloid change is negligible and the lipoid in the epithelium the essential feature I believe it will take far more proof than is yet available to persuade unprejudiced observers of this view.

That lipoid nephrosis and the waxy kidney are entitled to a position in renal classification distinct from nephritis may well be claimed, though Schlayer and others believe there is an uninterrupted series of gradations linking them together. On the other hand, I do not see any justification for grouping them with ordinary degenerations of the tubular cells when no other lesions and no dropsy are present.

I do not believe that a total of some dozen reported cases should so impose the character dropsy on many thousands of cases that have no dropsy, that the name of the group to which they all belong should suggest dropsy whenever it is used.

So far as carrying this error over to nephritis by the term "nephrotic component" so that it pervades the whole domain of Bright's disease I can only wish I had many voices instead of one to raise in protest and beg of you to purge our vocabulary of these sorcerer's words.

If we remove ourselves from the heat of the discussion and look over the work that has been done on nephrosis dispassionately there are only two new contributions in the whole mass.

First, a few cases have been shown to occur where the main

lesion is lipoid in the renal epithelium and the main symptoms dropsy and much albumin. These cases are not pure for some changes in the glomeruli or in the stroma have been present in all of them.

Second, some relationship between dropsy and lipoid has been demonstrated in certain cases. How significant this may prove depends on much more study.

Whatever its disadvantages "nephrosis" has probably come to stay and the best we can do is to appreciate the shortcomings of the conception and avoid as far as we can the misconceptions to which it constantly leads us.

If those who favor the conception and use the term "nephrosis" would only make this diagnosis, as they properly should, in nearly every case of pneumonia, measles, and bacterial infection, it would at least put an end to the idea that dropsy is an essential or usual symptom of nephrosis. In these conditions, moreover, the diagnosis is practically certain to be correct.

On the other hand, in the case that forms the text for this paper to make a diagnosis of nephrosis without qualification is altogether inadequate. There is indeed one chance in many thousand that the case may be one of *lipoid* nephrosis. If the patient has suffered from tuberculosis or long suppuration she may well have a waxy kidney. The overwhelming probability, however, is that an autopsy would reveal a nephritis and not a nephrosis.

CLINIC OF DR. LLOYD F. CRAVER

MEMORIAL HOSPITAL

DIAGNOSIS AND TREATMENT OF THYMOMA

THAT the presence of a thymoma is frequently not suspected and may not be known until a roentgen film or an autopsy has disclosed it, is the impression gained from a survey of case reports of the past decade and the Memorial Hospital cases. Thus in several of our cases the diagnosis of mediastinal tumor was apparently not made until a roentgen film of the chest had been taken, and several instances have been found in the literature in which the thymic tumor was reported as an unexpected postmortem finding.

SIGNS AND SYMPTOMS

It is well, therefore, to call attention to those slight early signs of thymoma which may be overlooked or misinterpreted. Foremost among such signs is puffiness about the eyelids and fulness at the base of the neck. Nephritis may be suspected by the physician, because of the swelling about the eyes; or the patient may ascribe the swelling of the neck to "becoming stout"; or, occasionally his physician may accuse him of having a goiter. A peculiar pink discoloration of the eyelids, resembling theatrical make-up, in one case of thymoma, is recorded by Herriman and Rahte. At the same time, or later, the patient or physician may notice a swelling of the veins on the chest wall usually in the upper part in front, at the center, or spreading outward toward the shoulders.

At this stage there may be no other definite symptoms. There may be some weakness, nervousness, loss of weight, vague pains in the chest, dyspnea, or cough. Such symptoms,

however, are variable, may be absent, or may be present singly or in various combinations, especially in the untreated cases. Later, most of these symptoms may be found when the results of pressure by the tumor in the anterior mediastinum become plainer. There is then more swelling of the face and neck, at times causing a hideous maskelike facies, red or blue from congestion of the superficial vessels. The whites of the eyes become blood shot. The congestion rapidly increases when the patient lies down. The swollen veins on the front of the upper chest increase in caliber, number, and extent. The arm veins may be swollen and edema of one or both hands or arms may appear.

Cough is variable. Bloody sputum is rare. Difficulty in breathing, because of narrowing of the trachea due to pressure by the tumor, may advance to loud stridor, extreme cyanosis, and death from suffocation.

Enlargement of lymph nodes above the clavicles or in the axillae may be early, late, or absent throughout the course. The "signal node" in the left supraclavicular space near the end of the thoracic duct, is not, apparently, enlarged earlier or more frequently than other nodes in the supraclavicular fossae. Axillary nodes, if involved at all, usually become so later than the supraclavicular nodes.

The characteristics of the involved nodes vary considerably, when one compares different cases. In some they are small, almost soft, separate, and freely movable, and only one may be felt above or behind one or the other clavicle. Other cases will present extensive hard fixed masses of confluent nodes. In such instances the patient may have considerable pain in the neck or down one or both arms from pressure on the brachial plexus. It is especially in cases of carcinoma of the thymus that one finds such hard nodes. Similar masses of firm, rather than stony hard, consistence may be found in cases of thymic Hodgkin's disease.

Together with stony hard nodes, a more chronic-looking and severe type of venous stasis appears in the cases we have come to recognize clinically as radioresistant. In these patients the chest wall in front and on the sides may show a remarkable pic-

ture—a network of dark blue veins, often with a well-defined edge at about the level of the diaphragm. The face and neck in these cases is chronically dusky red or blue, rather than pink.

A moundlike tumor over or beside the sternum develops in some cases of thymoma. Such a tumor is produced by direct extension of the primary growth through the chest wall, either through the intercostal spaces at the edge of the sternum, or, at times, by actual infiltration and partial destruction of the sternum.

The rarity of metastases of thymoma below the diaphragm is mentioned by Herriman and Rahte, who are not, however, correct in claiming that their case, reported in 1929, is the fourth on record with metastases below the diaphragm. Other reports than those they mention are found of metastases to the liver and kidneys. W. Brown reports a case under the rather misleading title, "Thymoma Simulating Abdominal Tumor." In his case, a male child of two years and five months, a primary thymic tumor not much larger than a normal thymus was not discovered until the autopsy was done. Besides a metastasis to the kidney cortex and one small discrete mesenteric node, it had produced a bulky metastatic tumor mass in the mesentery of the small bowel, the chief finding during life. In one of the Memorial Hospital cases bulky tumors have appeared in different parts of the abdomen from time to time, disappearing rapidly following treatment with the roentgen rays.

Herpes zoster has been noted in two of our cases. In both instances the area of skin involved corresponded roughly in its level of innervation from the spinal cord to the level of the main tumor mass which was present at the time of the attack of herpes. Also, the herpes occurred on the same side as that on which the main bulk of tumor was then present. Thus, in one case, the band of herpes extended about the midthoracic region on the left. This boy had a fairly bulky thymoma mostly to the left of the midline. In the other case a bulky metastasis had developed in the right upper quadrant of the abdomen, and the band of herpes developed on the same side and at the same level.

PHYSICAL SIGNS

It is difficult to believe that a careful examination of the chest could have failed to disclose the presence of abnormal dulness over the sternum in some of the cases reported in the literature, in which a large thymoma was discovered at autopsy. Moreover, in some instances the presence of fairly large supraclavicular nodes involved by tumor, which it would seem must have been readily palpable, is not mentioned except in the autopsy protocol. The conclusion drawn from the above observations in the literature is that to discover a thymoma one must regularly include in a chest examination careful percussion of the sternum, palpation for supraclavicular nodes (especially behind the clavicles), and for axillary nodes, and a good roentgen film.

Most thymomas of any considerable bulk are so closely applied to the anterior chest wall under the sternum that by careful percussion one can usually quite readily map out with fair accuracy the same size and contour that will be revealed on the roentgen film. This retrosternal dulness may be the only physical sign. It may vary considerably in intensity, location, and extent. For example, one may find an area 5 cm. in diameter of dulness to one side of the manubrium; the lower half of the sternum may be dull; there may be a rectangular zone of dulness all to one side of the sternum; or, as in the typical case, there is a rectangular, globoid, or pyriform area of dulness extending beyond each edge of the sternum, capping the heart dulness as the shadow of the thymoma on the roentgen film caps the pericardial shadow.

Most of the other common findings on examination have been sufficiently indicated above in describing the symptoms (dilatation of the veins over the chest, increased congestion of the face in the recumbent posture, swelling of neck, face, and upper extremities, enlarged soft, firm, or hard supraclavicular or axillary nodes, etc.).

Some additional findings of interest may be noted here. Exophthalmos is occasionally seen. A persistent tachycardia of strikingly uniform rate from day to day and week to week is at

times found. Bradycardia has not been observed in the Memorial Hospital cases.

Quite frequently the breath sounds over the upper lobes of the lungs anteriorly show a distinct change toward the bronchovesicular type. This seems to be a mechanical effect produced by the presence of the mediastinal mass. D'Espine's sign is frequently found.

The esophagus may show, in the later stages, partial, or, rarely, complete obstruction. At times it may become markedly deviated from its normal course.

As the thymoma extends it may produce broad flat sheets of tumor tissue over the pericardium and parietal and visceral pleura. It frequently invades the heart muscle. Pleural effusion, serous, or serosanguineous, is a common complication.

Extensive pulmonary metastases, appearing on the roentgen film usually as discrete, well-circumscribed, round or oval dense shadows, may develop, and may give few or no symptoms at first. It is therefore advisable to examine the chest at frequent intervals, and particularly to take frequent roentgenograms, since this type of metastasis is more readily detected by means of the roentgen rays than by physical examination. Moreover, the type of tumor which produces such metastases is almost certain to be so radiosensitive that their early detection and prompt treatment will be amply rewarded by their rapid regression and often complete disappearance.

Of unusual interest at Memorial Hospital have been the bone metastases of thymoma. These have appeared in bizarre forms, making early recognition difficult. Reports of bone metastases are comparatively uncommon in the literature of thymoma. Experience in this disease, as in Hodgkin's disease, lymphatic leukemia, and lymphosarcoma at the Memorial Hospital, has shown that one must be on the alert for bone involvement in parts of the body distant from the main tumor process. The earliest appearance on the roentgen film of bone metastases in these diseases may be so slight as to be easily overlooked. Two or three scattered minute areas 2 to 3 mm. in diameter of decreased density in a bone, over which there is pain and marked

local tenderness, is the common early finding. Later these areas may enlarge and coalesce, but seldom form any large area of destruction. Yet with such minute lesions terrific sharp pain may dominate the picture, and exquisite definitely localized tenderness to pressure over the involved area of bone is usually present.

Intracranial metastases to the region of the left cavernous sinus, and later to the left cerebellum were indicated clinically by the symptoms which developed in one patient. These symptoms rapidly disappeared following radiation to the areas believed to be involved and have not returned.

DIAGNOSIS

The differential diagnosis of thymoma in the majority of cases can be made with considerable certainty on a clinical basis alone. At times it remains uncertain even after autopsy and the study of microscopical sections.

Early Diagnosis.—Nowadays the earliest diagnoses of thymoma as a rule follow the unexpected finding on roentgen films of widened mediastinal shadows in cases in which chest films have been made in a routine search for the cause of some vague symptom, such as fatigue, nervousness, indefinite pains in the chest, cough, or dyspnea. Such patients may present no external signs of the disease, and percussion may reveal but little increase of mediastinal dulness. The typical appearance on the films of such early cases of thymoma is of a definitely widened anterior mediastinum, with fairly straight lateral borders. The shadow as a rule caps the pericardial shadow. Such cases are less numerous in the material coming to Memorial Hospital than the somewhat more advanced ones, who present about the following clinical picture:

Having had various of the above-mentioned indefinite symptoms for a variable period, the patients discover puffiness of the face and neck, dilated veins over the chest wall, increasing dyspnea or cough. Percussion now reveals distinctly a considerable widening of the mediastinal area of dulness anteriorly, with straight or convex lateral borders.

Carcinoma of the lung almost never gives quite this picture. Much more frequently in the cases of carcinoma of the lung is there a history of chronic cough, and hemoptysis is a much more frequent symptom than with thymoma. Severe pain in the chest occurs much more often in cases of carcinoma of the lung, and the patient becomes cachectic much more rapidly.

Sometimes, to differentiate between aneurysm and thymoma is a most difficult task, without awaiting the further course of the disease. The mediastinal mass, intimately surrounding and compressing, as it does, the large vessels, may seem on fluoroscopy to show a true expansile pulsation, so that, if there is no tumor-like adenopathy in the neck or axilla, and especially if the Wassermann test should happen to be four plus, it is hard to convince anyone that the process is not an aneurysm. When the typical physical signs of aneurysm are lacking, it is well in such doubtful cases to apply the therapeutic test by means of one adequate dose of radiation with either the radium pack or high-voltage roentgen rays. Such a test will probably do an aneurysm no harm, and, since most thymomas are very radio-sensitive, inside of a month the diagnosis will usually be made.

Seldom in cases of thymoma is there any noticeable inequality of the pupils, unilateral flushing, or perspiring of the face, or inequality of the radial pulses.

Sometimes when a moundlike mass is present over or alongside the sternum it will raise a suspicion of aneurysm penetrating the chest wall, because of transmitted pulsation from the aorta beneath; or it may have to be distinguished from gumma or tuberculous abscess arising from bone. The other features of the case will usually serve to make the differential diagnosis.

Biopsy.—The biopsy for diagnosis is of minor value in this group of diseases. It is certainly not justifiable to explore the mediastinum for the purpose of taking a biopsy, and in many of the cases a considerable time elapses before an accessible lymph node in the supraclavicular space or axilla becomes involved. When such nodes do become involved they are often so matted together that to do a biopsy involves taking a wedge out of actively growing highly malignant tumor, breaking its capsule,

and thus causing the risk of fungation of tumor tissue through the wound, infection, necrosis, and hemorrhage; or the subsequent scar formation may bind down the skin and produce contracture of the neck. When the tumor has penetrated the chest wall and is covered by intact freely movable skin it would also seem inadvisable to do a biopsy in this location because of the rupture of the restraining tissues that would be produced by the knife. Possibly further experience with diagnostic needle puncture may show that this procedure will yield a fair number of satisfactory microscopical specimens with less trauma to the tumor and the restraining tissues overlying it.

When a loose discrete node is involved it may probably be removed safely; yet it may fail to show a structure typical of the main tumor.

TREATMENT

There are three main requisites for the proper management of a case of thymoma.

First, to be able to deliver an adequate dose of radiation to any depth within the body.

Second, to continue to observe the patient at frequent intervals as long as he lives.

Third, to be alert for the appearance of metastases under strange guises.

Surgical treatment of thymoma deserves mention only to be condemned. Among the reports of surgical attempts to deal with malignant thymomas is that of Sheen, Griffiths, and Schölberg in 1911. Two cases of "small round cell sarcoma" of the thymus were operated on. In one case the manubrium was split and separated from the body of the sternum. This patient was relieved of dyspnea for a short time. Their second case was not relieved by a transverse incision of the deep cervical fascia.

In view of the inaccessibility of most thymomas, their usual high degree of malignancy and the known radiosensitivity of the great majority, attempts at surgical intervention seem foolhardy. Yet the literature indicates (Voges, Zajewloschin) that here and there such attempts are still being made.

Most cases of thymoma will require repeated radiation. Therefore, in order to conserve the skin and yet be able to radiate the deepest portions of the tumor adequately, a penetrating type of radiation must be used, such as only the high-voltage roentgen apparatus, or the radium emanation or radium pack at a distance can supply. The pack should be filtered by the equivalent of 2 mm. of brass and should be used at a distance from the skin of at least 6, preferably 10, and at times even 15 cm. The high-voltage roentgen rays should be generated by not less than 175, and preferably 200 kilovolts; the filtration should be the equivalent of 0.5 mm. of copper; and the target-skin distance preferably 50 cm. It is of great practical advantage when treating a dyspneic, orthopneic patient to have a water-cooled high-voltage machine, so that in five minutes one can give the equivalent of about thirty-five minutes' treatment with the ordinary air-cooled machine.

It was recognized years ago that in general the thymomas are remarkably radiosensitive tumors. Yet here and there some cases after irradiation stood out as complete failures, and others showed less satisfactory results than were expected. Until recently such failures have often been ascribed either to improper technic or to the advanced stage of the disease at the beginning of treatment, without any very critical weighing of such judgment. We now recognize that while the majority of thymomas are radiosensitive, and some of them to a truly remarkable degree, it is a fact that some are distinctly radioresistant. It has even seemed possible in the past year or two to predict with some success on a clinical basis what the response to irradiation in a given case is likely to be. The patient who enters showing a widespread fine network of dark blue veins on the chest wall, a more dusky type of cyanosis of face, conjunctivae, and oral mucous membranes, or many small hard shotty supraclavicular nodes, usually has a poor prognosis. On the other hand, the patient with a single moundlike tumor mass over or at the edge of the sternum usually has a good outlook for primary regression of his tumor. The enlarged veins on the chest wall of the favorable cases are coarser, lighter blue channels, and the color of the

face, while showing perhaps some congestion, is of a lighter hue than in the unfavorable cases. The consistence of the palpable involved lymph nodes in the unfavorable cases may be said to resemble that of nodes involved by squamous carcinoma, while the nodes in favorable cases are softer.

The procedure at Memorial Hospital in the treatment of a case of thymoma is as follows: If the history, physical examination, and roentgen study indicate only the presence of the mediastinal tumor, without discoverable metastases, the mediastinum is treated anteriorly with the radium or emanation pack or the high-voltage roentgen rays. The emanation pack dose is about 20,000 millicurie hours at 10 cm. from the skin. The roentgen-ray dose is about 450 ma. minutes at 50 cm. target-skin distance. The size of the portal on the skin depends upon the size of the tumor; usually the entire mass is included in one beam. Preferably these doses are divided, so that about one third is given every other day.

The usual radiosensitive type of thymoma may show relief from symptoms within a few hours after the first fraction of treatment has been given; in a few days the betterment may be striking, and in a few weeks all symptoms may have disappeared. Often in one to two months the tumor is no longer visible on the roentgen film. It is well to await for a short time the result of this first treatment, so as to know more certainly what type of tumor in reference to radiosensitivity one has to deal with, and to spare the patient the constitutional effects of too much irradiation of the body at one time. Within about two weeks further similar treatment may be given over the mediastinum posteriorly.

If within one or two months the tumor has disappeared, the question arises, how often to repeat the treatment. Some cases have been known to go for years with no further treatment to the mediastinum without showing local recurrence. However, it is probably not safe as a rule to rely upon this first series of treatments for complete sterilization of the tumor, therefore it is felt best to repeat the irradiation of the mediastinal area once or twice at least at intervals of say one to three months.

If at the time of the first treatment involved nodes are found in the supraclavicular space, they may in some cases be included in the mediastinal field when it is irradiated, but perhaps had better be treated by a separate exposure, which may be directed downward and inward so that it, too, delivers some radiation to the mediastinum.

If the tumor is of the less radiosensitive type one can only attempt to restrain its growth as much as possible and for as long a time as possible by judiciously repeated cycles of irradiation. At times it seems of advantage to change from roentgen rays to the radium pack. One should keep palliation ever in mind as the aim in such a case, being guided by the patient's condition, and not letting it seem that the treatment is worse than the disease. Such a conservative course may be rewarded months later by a gradual regression of the tumor, or the patient may be kept in fair comfort for a long time. As indicated above, however, the occasional very resistant case will fail utterly to respond and will rapidly become worse and die of asphyxiation. The cases that are capable of responding can be made to do so without damaging the skin when one uses the penetrating sort of radiation described above.

Following the initial regression or disappearance of the tumor the patient should not be allowed to remain away for long periods, even if there is no evidence of disease, but should be seen at intervals of three to six weeks. A tumor which responds so readily will also recur readily, and bulky recurrences and metastases are prone to develop within a short time, yet sometimes with so few symptoms at first that the patient may not be aware of their presence. Roentgen films of the chest should be taken at frequent intervals.

The further observation of the case requires alertness for all sorts of symptoms of possible recurrence or metastasis. Pain in the head, back, chest wall, pelvis, or thighs should be suspected as indicative of metastasis, especially to the bones. Cerebral symptoms—diplopia, nystagmus, deviation of tongue, dizziness, staggering and vomiting—appeared in one case. Gastrointestinal disturbances may unexpectedly be found to be caused

by a huge abdominal mass that may have developed in the few weeks since the previous observation. Constipation may be found to be due to a bulky diffuse infiltration by tumor tissue in the pelvis, surrounding and compressing the rectum to a narrow slit. Cough, pain in the chest, or dyspnea may be referable to a recurrence of the thymoma or to the lung or pleura metastases or extension.

The type of thymoma which gives rise to such manifestations is the radiosensitive type, and therefore prompt discovery and treatment of the metastases will be followed by their rapid disappearance, provided they are accurately localized and the beam of radiation accurately directed toward them.

CASE REPORT

A. F. M., a man thirty-nine years old, married, a native white American, first came to Memorial Hospital March 22, 1928.

Family history negative.

Past history negative except for slight occasional indigestion.

Present History.—Onset six months previously with a sensation of substernal pressure. This recurred in four or five attacks during a period of two or three months, was worse at night and was relieved by belching a small amount of gas. Cough had begun three months previously, had increased, and had become productive during the previous ten days. Wheezing on inspiration had begun six weeks before and for the previous month he had been unable to lie comfortably on his back or left side. He had lost 15 pounds recently and had noticed some dysphagia for solid foods. He had not observed any swelling of the neck or enlarged veins on the chest wall.

The examination showed the following: the patient, a man of small stature, and dark complexion, was up and about, and seemed in fairly good general condition. His weight stripped was 99½ pounds. The neck showed a firm ovoid movable mass, 4 x 6 cm. at the left base, anteriorly; the trachea seemed to be displaced about 0.4 cm. to the right.

Percussion of the chest disclosed marked widening of the area of mediastinal dulness anteriorly, extending beyond the midclavicular line on the left, not so far on the right. The lungs had bronchovesicular breath sounds over the left apex, and occasional sibilant and sonorous râles elsewhere.

The heart seemed somewhat enlarged. Its rhythm was regular, but its rate was 126 with the patient in sitting posture. The rest of the physical examination was negative. Urine was negative. Blood count: hemoglobin, 85 per cent; red blood cells, 4,360,000; white blood cells, 7200; polynuclear cells, 75 per cent; large lymphocytes, 9 per cent; small lymphocytes, 5 per cent; transitional cells, 5 per cent; eosinophils, 4 per cent. Wassermann negative.

Clinical Diagnosis.—Thymoma.

Roentgen examination of chest (Fig. 112) disclosed a broad shadow in the anterior mediastinum, capping the heart shadow, and having fairly clean-cut lateral borders. This finding was regarded as confirmatory of the diagnosis of thymoma.

Treatment and Course.—Within eight days a cycle of five high-voltage roentgen-ray treatments was given to the mediastinum, anteriorly and posteriorly.

The symptoms began to diminish before the cycle of treatments was finished. One week later the mass in the neck had almost entirely disappeared

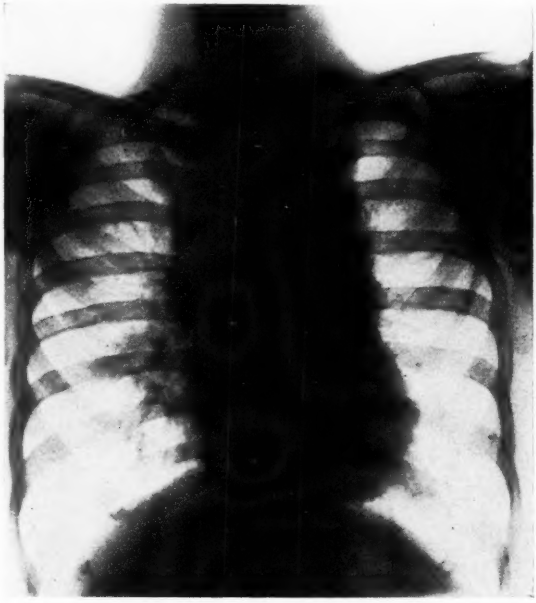

Fig. 112.—A. F. M., March 22, 1928. Thymoma before treatment.

and the roentgen film showed marked decrease in the size of the mediastinal shadow. One month after treatment the decrease in the shadow was much more marked (Fig. 113). The mass in the neck was gone, and the patient felt much improved, having only a slight cough and no wheezing.

Further cycles of treatment were given to the mediastinum two, seven, and eleven months after the first cycle.

Five months after the first cycle there was no evidence of a mediastinal mass (Fig. 114), and up to the present time (Fig. 117) there has at no time been any evidence of a return of the tumor in this location.

However, various complications to be ascribed to the tumor process

occurred and kept the patient incapacitated for work until April, 1929 thirteen months after he first came to Memorial Hospital. These sequelae can be only briefly described.

In August, 1928, five months after the first treatment, he had a severe pain for a few days in the left side and soon showed (Fig. 114) evidence of pleural effusion at the left base. This cleared up without treatment.

In September, 1928, he developed ptosis of the left upper eyelid, inability to turn the left eye to the left, with consequent diplopia on looking to the left, and dilatation of the left pupil. He was seen in consultation by Dr.

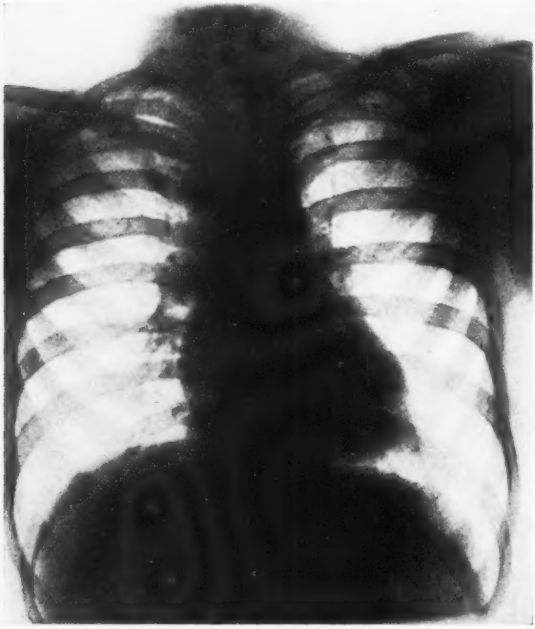

Fig. 113.—A. F. M., April 26, 1928. One month after treatment of thymoma.

George H. Hyslop, who stated that there was probably a metastatic lesion in the region of the cavernous sinus, and recommended irradiation of this area. Following treatment to this region through the temples by roentgen rays, the symptoms began to disappear promptly and within a week were practically gone.

The next month, October, 1928, following the third cycle of treatment to the mediastinum, he developed a typical pericarditis, and a recurrence of the pleurisy at the left base. His pulse rate increased to 150, but responded well to digitalization by mouth. A pleural friction rub then developed at the

right base, posteriorly. Over the left tenth rib a tender fusiform swelling 7 cm. long and 3 cm. wide appeared. It was regarded as a rib metastasis, although because of the location no definite change in this rib could be seen in the roentgen film. This swelling disappeared a few days after irradiation.

About the end of November, 1928, a similar tumor appeared over one of the lowermost ribs on the right side, posteriorly. It disappeared, also, very rapidly, following irradiation.

At this time the patient had suddenly become very dizzy and had a pronounced staggering gait. The eyes showed bilateral nystagmus, more

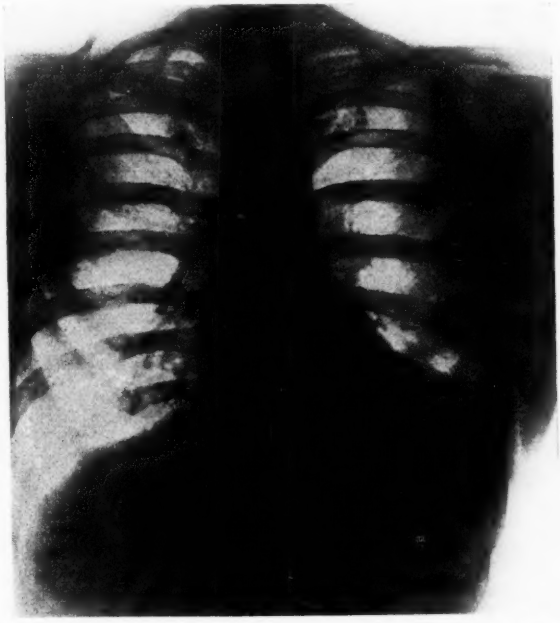

Fig. 114.—A. F. M., August 28, 1928. Five months after treatment of thymoma. Note absence of mediastinal widening. Evidence of pleurisy at left base.

when looking to the right, and slight vertical nystagmus. Occasionally, there was vomiting, apparently induced by the dizziness.

Doctor Hyslop again saw him and stated that the symptoms indicated involvement of the left cerebellum. Without treatment the dizziness cleared up, but about three weeks later the patient complained of severe generalized headache, thickness of speech, difficult deglutition, and said that he had bitten his tongue several times on its right side. The tongue showed a marked deviation to the right.

Small fractions (about $\frac{1}{3}$ erythema doses) of high-voltage roentgen rays were given to the left occipital region, directed toward the cerebellum, on December 21 and 26, 1928. A week later the cerebellar symptoms had almost entirely disappeared and he had gained 5 pounds.

There was still some evidence of pleurisy at each base.

During all this time since the attack of pericarditis, there had been a persistent tachycardia, rate 96 to 120.

In January, 1929, the roentgen film disclosed a large metastatic tumor mass overshadowing the lateral border of the heart (Fig. 115). This area

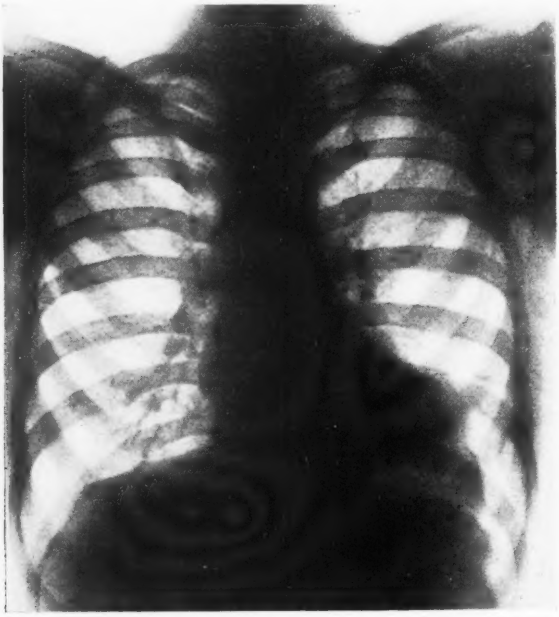

Fig. 115.—A. F. M., January 2, 1929. Note large tumor mass at left side of heart.

was treated on January 9th, 14th, and 17th. The picture made on January 21st showed a marked diminution in this mass (Fig. 116).

In March, 1929, diplopia recurred, to a less extent than before. It again disappeared within a few days following roentgen treatment through the temples.

Later in March, there was found at the site of the original mass at the base of the left side of the neck a small firm pea-sized node. It was irradiated and soon disappeared.

On April 1, 1929 the patient was able to return to work part time. The tachycardia gradually disappeared, and subsequently and up to the present time (June, 1930), he has been able to work full time. For a year his only symptoms were occasional very slight pains in various regions, such as the perineum, the right knee, the left upper arm, and the right occiput; but these areas showed no other evidence clinically or roentgenographically of involvement. However, in May, 1930 the pains about the pelvis became somewhat more annoying. It was then discovered, as a result of taking roentgenograms of his entire skeleton, that at each acetabulum there was an area of slight yet unmistakable irregular bone absorption. This change was more marked on the left side. Irradiation of these areas has been followed promptly by relief from pain. It is too soon to judge whether treatment has effected any repair process in the bone. His general health has not deteriorated since his return to work over a year ago. He now weighs 110 pounds, stripped. He continues under frequent observation, as experience in this and other cases indicates the importance of watching for unusual manifestations of the disease.

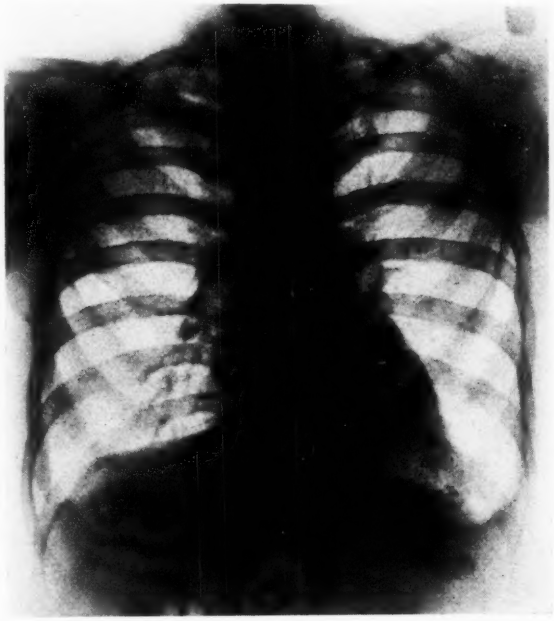

Fig. 116.—A. F. M., January 21, 1929. Four days after last of three fractional roentgen treatments over precordium; compare with Fig. 115 to note diminution in size of metastatic tumor mass at left base.

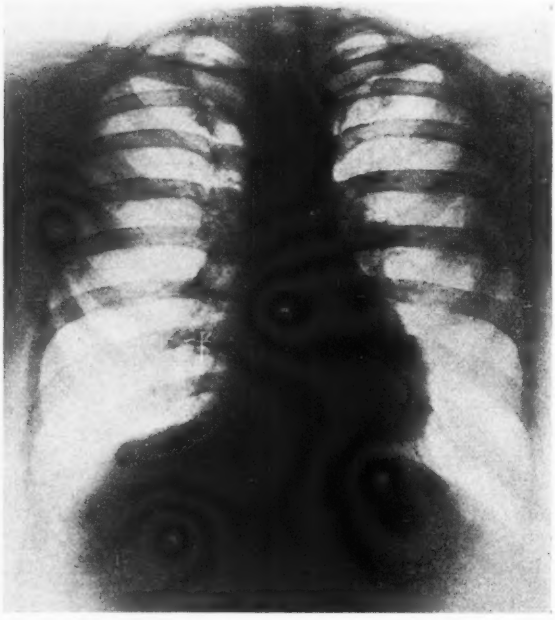

Fig. 117.—A. F. M., January 10, 1930. Showing present condition. Thymoma one year, ten months after first treatment.

SUMMARY

The diagnosis of thymoma may be made with fair assurance during the patient's life in a majority of cases, on the basis of symptoms, physical signs, and roentgenographic findings.

The treatment should be irradiation with high-voltage roentgen rays or the radium or radium emanation pack.

Cases of thymoma should be closely observed at frequent intervals indefinitely, since metastases or extensions of the tumor may give rise to many unusual complications.

BIBLIOGRAPHY

Bell, E. T.: Jour. Nerv. and Ment. Dis., 45, 130, 1917.
Brown, S. E.: Arch. Path. and Lab. Med., 2, 822, 1926.
Brown, W.: Brit. Med. Jour., 2, 101, July 21, 1928.

Courtois-Suffit, de Jong, S. I., and Liége: Bull. de l'assoc. franç. pour l'étude du cancer, 15, 333, 1926.
Evert, J. A.: Minn. Med., 8, 730, December, 1925.
Ewing, J.: Surg., Gynec., and Obst., 22, 461, 1916.
Foot, N. C.: Amer. Jour. Path., 2, 33, January, 1926.
Grandhomme, Fr.: Dissertation Heidelberg, 1900.
Groover, Christie, Merritt, and Coe: Jour. Amer. Med. Assoc., 85, 1125, October 10 1925.
Harvier, P.: Bull. et mém. soc. méd. des hôp. de Paris, 45, 374, 1921.
Helvestine, F., Jr.: Arch. Surg., 9, 309, 1924.
Herriman, F. R., and Rahte, W. E.: Amer. Jour. Path., 5, 29, January, 1929.
Jacobson, V. C.: Arch. Int. Med., 31, 847, 1923.
Janeway, H. H.: Ann. Surg., 71, 460, 1920.
Jones, A. C.: Trans. Amer. Laryng., Rhinol., and Otol. Soc., 34, 478, 1928.
Kaijser, R.: Act. path. et microbiol. Scandinav., 4, 221, 1927.
Landgraf, C.: Inaug. Dissert., Berlin, 1914.
Lemann, I. I., and Smith, J.: Arch. Int. Med., 38, 807, 1926.
Lenz, R.: Wien. med. Wchnschr., 78, 262, February 18, 1928.
Matras, A., and Priesel, A.: Beitr. z. path. Anat. u. allg. Path., 80, 270, August 1, 1928.
Miller, J.: Canad. Med. Assoc. Jour., 16, 810, 1926.
Plank, T. H.: Physical Therap., 45, 240, May, 1927.
Pool, E. H.: Surg. Clin. N. Amer., 5, 34, February, 1925.
Rubaschow, S.: Virch. Arch., 206, 141, 1911.
Schmidt, E. A.: Arch. Phys. Therapy, 7, 558, 1926.
Sheen, W., Griffiths, C. A., and Schölberg, H. A.: Lancet, 2, 1253, November 4, 1911.
Strauss, S. G.: New York Med. Jour., 110, 646, October 18, 1919.
Symmers, D., and Vance, B. N.: Arch. Int. Med., 28, 239, September, 1921.
Vangeon, P.: Thèse de Paris, 1921.
Voges, H.: Frankfurter Ztschr. f. Path., 33, 501, 1926.
Young, G. J., and Spalding, J. E.: Jour. Med. Soc. New Jersey, 25, 609, October, 1928.
Zajewloschin, M. N.: Virch. Arch., 254, 63, 1925.

CLINIC OF DRS. JOHN WYCKOFF AND
ARTHUR C. DEGRAFF

FROM THE THIRD (NEW YORK UNIVERSITY) MEDICAL DIVISION
OF BELLEVUE HOSPITAL

THE OCCURRENCE OF RAPID ECTOPIC RHYTHMS AS A PROBLEM IN THE DIAGNOSIS OF ACUTE CORONARY OCCLUSION

THE clinical picture of coronary thrombosis has been described so frequently, within recent times, that it is familiar to everyone. Several cardinal points in the diagnosis might, however, be emphasized: The sudden onset, usually with severe agonizing precordial or epigastric pain, and the fear of impending death; the severe prostration with a fall in blood pressure, fever, and leukocytosis, occasionally a pericardial friction rub, and changes in the form of the electrocardiogram. That some of these signs may also occur in other conditions and be confused with coronary thrombosis has been pointed out by Scott, Feil, and Katz.[1] They pointed out that the coronary T wave of the electrocardiogram was very much of a misnomer and could occur in other conditions, for instance, in pericarditis with effusion. Since then Kountz and Gruber[2] have produced all the so-called "pathognomous electrocardiograms" of coronary thrombosis by varying grades of general anoxemia.

Not only might reliance upon electrocardiographic changes lead us astray, but the clinical picture with severe pain of sudden onset and a drop in blood pressure might do so. Such a clinical syndrome occurs very frequently at the onset of a paroxysm of a rapid ectopic rhythm such as paroxysmal auricular tachycardia. The following case reports illustrate very clearly how difficult it is to distinguish between the onset of such a rhythm and the more serious condition of coronary thrombosis.

CASE REPORTS

Case I.—L. T., age twenty-nine years, female, married, admitted to the hospital on November 14, 1929, markedly dyspneic, orthopneic, and cyanotic, covered with a profuse perspiration and complaining of severe precordial pain and palpitation.

She gave a history of having had an attack of palpitation following childbirth at the age of twenty-five. There was no precordial pain at that time. Since then she had similar attacks on an average of once a year. These attacks would last a few hours and then would stop suddenly. Occasionally they would come on when the patient was asleep and wake her up. Last summer the attacks became more frequent, occurring about once a month and at this time they began to be accompanied by precordial pain which with each succeeding attack became more severe. The present attack came on suddenly while the patient was seated in a chair at home. The precordial pain was agonizing in character and although morphine was given before her admission to the hospital there was no diminution of the pain.

On physical examination she was seen to be markedly dyspneic, orthopneic, and cyanotic. Her forehead was covered with profuse perspiration. Her skin was ashen gray in color. The veins of the neck were visible and pulsating at a very rapid rate which could not be counted. There were moist râles at both bases of the lungs. The heart: The P. M. I. was neither visible nor palpable. The apex beat was heard best in the fifth left interspace 12.5 cm. to the left of the midsternal line outside of the midclavicular line. The sounds were of poor quality, almost fetal type. No friction rub was heard. There were no murmurs. The rhythm was rapid and regular, the rate 180 per minute. Pressure over the carotid sheath over the eyeball produced no change in rate. There was no edema of the lower extremities. The pulse was so feeble and weak that no blood pressure reading could be obtained. The temperature was 101 F. on admission and ranged between 99 and 100.2 F. for the next four days; then gradually declined. The electrocardiogram (Fig. 118, A) showed a tachycardia probably of auricular origin with intraventricular block. The blood count showed 14,000 leukocytes with 84 per cent. polymorphonuclears on the day of admission. On the next day the total leukocyte count was 29,400 with a polymorphonuclear count of 84 per cent.

On the next day the patient's condition was no better. Her skin was cold and clammy. She was very dyspneic and orthopneic, her pulse was feeble and very rapid. At 8.45 P. M. on November 15, 1929 the heart rate suddenly dropped to 120 per minute and an immediate improvement was noted in the general condition of the patient. The electrocardiogram taken at this time (Fig. 118, B) showed an A-V nodal rhythm with intraventricular block. At 10.30 P. M. of the same day her blood pressure was 126/94 and the heart rate was 84 per minute. The next morning only a few moist râles were noted on physical examination of the chest. There was very little, if any, cyanosis and no dyspnea when at rest. The patient's condition improved rapidly so that by November 18th there were no signs or symptoms of failure. An electrocardiogram of this date was normal except for a deviation of the electrical axis to the left and a shallow inversion of the T wave in lead one (Fig.

118, C). On November 23d the patient suddenly developed a rapid heart rate of 230 per minute. She appeared in shock, her skin was pale, extremities were cold, lips cyanotic, and the pulse was very feeble. There was severe precordial pain. At 11.15 A. M. she was given 5 grains of quinine and urea hydrochloride intravenously and at 11.45 A. M. another 5 grains. Within three minutes after the last injection the ventricular rate dropped to 120 per

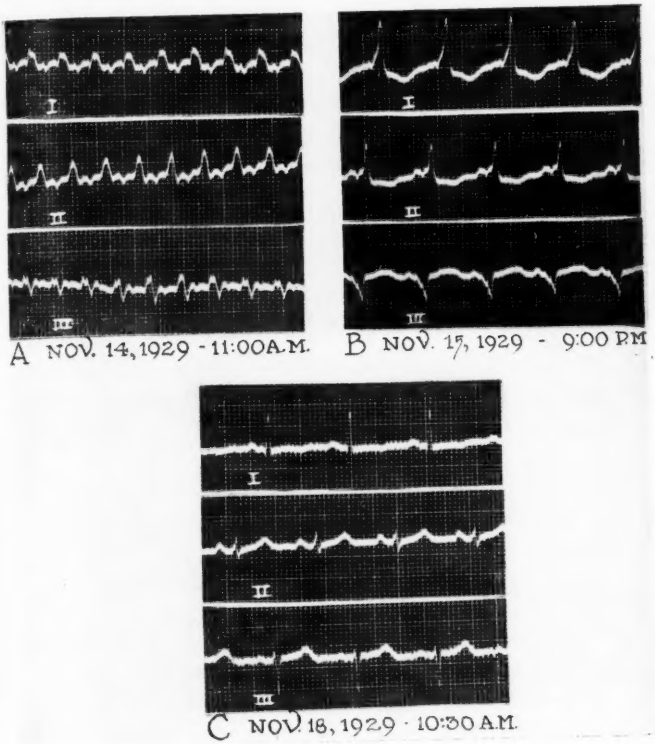

Fig. 118.—Electrocardiograms showing the changes from the rapid ectopic rhythm in A, to nodal rhythm in B, to regular sinus rhythm in C.

minute and the symptoms referable to acute cardiac failure cleared up almost immediately. At 3.30 P. M. the patient was comfortable with no complaints and her ventricular rate was 90 per minute. Once again on December 8th another attack of palpitation with precordial pain developed, and this again stopped after the administration of quinine and urea hydrochloride. The patient left the hospital on January 11, 1930, after being up and about

the wards for several days. There was no dyspnea or fatigue on effort and she was discharged as Class 2A, using the nomenclature of the American Heart Association. Her complete diagnosis on discharge was:

Cardiac A Unknown.
B Enlarged heart.
C Paroxysmal tachycardia.
D Class 2A.

We do not believe that a diagnosis of coronary thrombosis would be justified in this patient. She was only twenty-nine years old and a history of previous similar attacks with intervals of complete recovery of cardiac function make a diagnosis of coronary thrombosis a highly improbable one. The fact that we were able to observe her in two attacks while she was on the wards and that each time the precordial pain was accompanied by the onset of the rapid ectopic rhythm and that as soon as normal sinus rhythm was resumed the patient promptly recovered from all signs and symptoms of heart failure precludes the possibility of coronary thrombosis as the cause for each one of these attacks.

However, the diagnosis of coronary thrombosis was made by certain members of the staff when the patient was admitted to the hospital and it is not surprising because most of the classical symptoms and signs of coronary thrombosis were present. The attack was not precipitated by effort, a point upon which Levine[3] lays great stress in the diagnosis of coronary thrombosis. The first attack as well as subsequent attacks came on while the patient was quiet. She was either sitting in a chair or in bed. The patient's condition was suddenly changed from one in which she was comfortable to one of acute distress with precordial pain—she felt that something terrible had happened. The precordial pain was so severe that it was not relieved by morphine. The temperature was elevated and there was a leukocytosis. The pulse was so feeble that a blood pressure estimation could not be made. The electrocardiogram showed a rapid rate, a bundle branch block, and a relatively low potential in all leads, in addition to a sharp inversion of the T wave in leads one and two. All the classical signs and symptoms were present, except the pericardial friction rub, which is of course not always present

even in a proved case of coronary thrombosis. Thus we have a patient with an ectopic rhythm, a paroxysmal auricular tachycardia, whose onset simulates an attack of coronary thrombosis. A heart rate of such proportions will of itself cause a drop in blood pressure by shortening the length of diastole to such an extent that the period of rapid filling is encroached upon and there is a consequent fall in cardiac output per minute as well as per beat. This results in a drop in blood pressure.

Case II.—M. G., age forty-four years, was first admitted to the hospital on September 10, 1927 suffering with severe precordial pain, marked dyspnea, persistent vomiting and palpitation. On physical examination it was found that he was very dyspneic, cyanotic, and covered with a profuse perspiration. His pulse was weak, his blood pressure was 80/60, his heart rate was 220 per minute, the electrocardiogram showed a rapid rhythm, probably an auricular tachycardia with complete intraventricular block. His condition became steadily worse until the next morning at 10 o'clock when his heart rate sud-

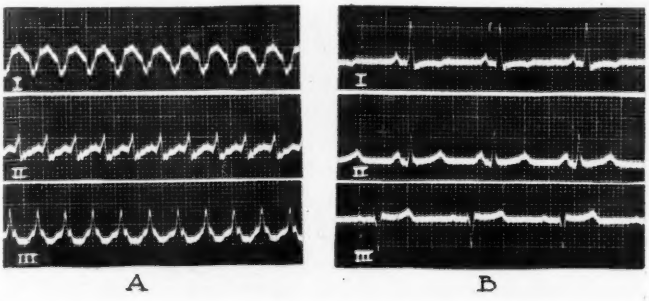

Fig. 119.—Electrocardiograms taken during and after the attack of paroxysmal tachycardia. A, During the attack; B, after the attack.

denly dropped to 80 per minute. All the symptoms disappeared and by evening the patient was feeling so well that he insisted upon getting up out of bed and going home. It was with great difficulty that he was persuaded to stay until the next morning. He had four similar attacks that year, each attack accompanied by severe precordial pain, in one case so severe that it was difficult to take his history. Two electrocardiograms are shown in Fig. 119, illustrating the rhythm during the attack and the normal rhythm when the attack had subsided. This patient has had many attacks since that time and is being watched at present in the Cardiac Clinic at Bellevue Hospital. Between attacks he is perfectly comfortable and is able to carry on his work as a street cleaner.

Two other cases might be cited briefly to illustrate that this condition occurs more often than just an occasional isolated instance.

Case III.—M. H., female, age thirty-five years. On the night of May 6, 1929, the patient had a sense of pressure over the precordium, which radiated to the left infrascapular region. On the morning of May 7th the pain became severe and remained so until hospitalization. The pain was accompanied by palpitation of the heart, chilliness, and cold sweat. On physical examination the patient was seen to be in shock. The heart rate was very rapid and an electrocardiogram identified the rhythm as an auricular tachycardia. As soon as the heart rate returned to normal rhythm all the symptoms were relieved and the patient promptly recovered.

Case IV.—R. M., female, age forty-three years. After a short sleep of one or two hours, the patient awoke with a severe pain in the chest. Her heart was beating violently and rapidly and the patient says she felt that she was going to die. After an hour and a half the palpitation ceased. The pain disappeared and although soreness persisted the patient was able to go back to sleep. She has had many similar attacks one of which was noted while in the hospital. An electrocardiogram taken during this attack showed an auricular tachycardia. This patient was also entirely well between attacks.

It is evident from the cases quoted above that paroxysmal tachycardia may occur without coronary thrombosis and be associated with symptoms which simulate it markedly. On the other hand, it must be remembered that coronary thrombosis is not infrequently associated with attacks of rapid heart action. As stated before this makes the differentiation sometimes extremely difficult.

The simultaneous onset of palpitation and pain did not occur in any one of eighteen proved cases of coronary thrombosis on the service of the Third Medical Division of Bellevue Hospital. One patient had auricular flutter on admission, but there was no history of its simultaneous origin with the pain. Three patients developed auricular fibrillation with rapid ventricular rates while under observation and one developed short runs of an ectopic tachycardia, probably of ventricular origin.

Every patient with paroxysmal tachycardia on the other hand does not develop precordial pain, 4 patients out of 13 did, a proportion large enough to consider this condition in the differential diagnosis of coronary thrombosis.

BIBLIOGRAPHY

1. Scott, R. W., Feil, H. S., and Katz, L. N.: The Electrocardiogram in Pericardial Effusion, Amer. Heart Jour., 1929, 5, 68.
2. Kountz, W. B., and Gruber, C. M.: The Electrocardiographic Changes in Anoxemia, Proc. Soc. Exp. Biol. and Med., 1929, xxvii, 170.
3. Levine, S. A.: Coronary Thrombosis: Its Various Clinical Features, Medicine, 1929, 8, 245.

CONTRIBUTION BY DR. GAYLORD W. GRAVES

CHILDREN'S MEDICAL DIVISION, BELLEVUE HOSPITAL

OBJECT LESSONS IN PEDIATRICS[1]

PEDIATRICS is the most general of the specialties. In a very true sense, the ordinary pediatrician is a general practitioner whose work is defined more closely by the age than by the disease of his patient.

Because the physiology of the infant and young child is concerned with structures that have not undergone degeneration, and with manifestations of resistance unmodified by active immunity, reactions in early life are more frank and more apparent than later. Children's illnesses are apt to be spectacular. Their recoveries are more rapid and surprising; their deaths more unexpected than those of other patients. Children, characteristically, while unstable and impressionable, seldom consciously simulate illness and more frequently than adults present reliable objective symptoms. On the other hand, although headache and stomachache are never to be disregarded in the case of a child, very often such subjective symptoms and the history are not of much greater value in pediatrics than in dermatology.

It may be inferred that the principal thing in the realm of pediatrics is to watch and listen and smell irrespective of the history of the case and finally to develop a diagnostic sense that even an English nursemaid's version cannot thwart. Not without developing the greatest respect for research and minuteness of investigation, the physician working with children thus ultimately comes to the belief that the best clinician is the one who has seen the most cases, and that the way to acquire pediatric knowledge is to have it thrust upon the doctor by daily experi-

[1] Presented in part before the Southside Clinical Society of Long Island January 15, 1930.

ence, without regard to that logical sequence considered so highly important in our voluntary training.

A typical early humiliating experience was afforded by a male infant about ten days old who had a high fever, swelling of one hand and an immediate history of hematuria. The homeopathic physician who had treated him had diagnosed rheumatism and nephritis. Resort to a sound volume on pediatrics seemed to justify a better guess that the baby had uric acid infarcts of the kidney and inanition fever. A few days later he died of umbilical hemorrhage complicating septicemia which probably was of umbilical origin without local evidence sufficient to cause suspicion.

Years later a two weeks' old baby girl, with a high fever and a slight bit of moisture at the umbilicus, which gave a smear of streptococcus, was presented at a clinic conference for diagnosis. The suggestion that she ought to have some joint manifestations of sepsis made little impression. Next day, however, she had an acute arthritis which was very apparent and eventually involved an elbow, a hip, and both knees. Seven weeks after the first signs of generalized sepsis this baby, who was twice discharged from the hospital as sufficiently well for dispensary supervision, was readmitted with fatal erysipelas secondary to otitis media and a positive blood culture of the organism which had been identified as the specific cause of the initial infection.

A nursing baby three weeks old suddenly terminated diarrhea of two days' duration and in the next thirty-six hours vomited bile-stained fluid, developed fever about 101 F., with extreme abdominal distention and rigidity, and failed to respond to enemata. Bloody mucus appeared upon rectal examination, and the case was diagnosed as one of intussusception. Operation disclosed a fatal spreading streptococcus hemolyticus peritonitis with enteroparesis that had simulated intestinal obstruction. No source of infection was discovered. This case had presented no sausage-shaped abdominal tumor and the vomiting had not been persistent.

An innocent-looking navel in a young infant, as the portal of entrance of general infection, is never beyond suspicion.

Of equally instructive character was the case of a six weeks' old Philippine Negro child weighing 8 pounds, 3 ounces at birth, brought at six weeks of age to Bellevue Clinic because of stiffness of the legs, of two weeks' duration. The skin over the upper half of both legs was swollen, tender, and shiny, without appreciable increased heat. This baby was too young to have scurvy and a bit too old for sepsis of the newborn. He had a perfectly typical syphilitic epiphysitis.

Because the Wassermann test in a syphilitic infant may be negative at birth and for some time thereafter, and because of the

uniformity of luetic bone changes that may be detected by x-ray, particularly at the upper ends of the tibiae, the x-ray should be used as routinely as the Wassermann and Kahn tests in diagnosing syphilis in infancy.

The manifestations of the so-called "deficiency diseases" in infancy are so varied that such cases almost never fail to be interesting. Accompanying illustrations emphasize points in this connection (Figs. 120, 121).

Fig. 120.—Infantile scurvy. (Seaside Hospital.)

A surgeon's baby, ten months old, developed a pseudoparalysis suggestive of poliomyelitis. Careful questioning elicited the story that several weeks earlier the baby had acted as if his legs hurt, but on a trip to Atlantic City his symptoms had ceased only to recur when he returned to New York. In New York he got pasteurized milk. In Atlantic City he had certified milk. Nowhere did he receive orange juice with any regularity, apparently because he disliked the taste.

Two days later when the infant was moving his legs freely, and the purple discoloration of his gums was disappearing, the surgeon on being

asked concerning the dosage of the orange juice, explained that since it had been determined that the baby had scurvy and since orange juice was indicated, it was immaterial whether the victim liked orange juice: he was now being given about 10 ounces a day.

For immediate effectiveness of clinical cure, this case of scurvy established a record.

Fig. 121.—Same case as Fig. 120 taken two months later. (Seaside Hospital.)

Mrs. S. telephoned to report that her infant daughter about nine months old had a sore leg which was suspected of having been bumped or twisted in the automobile. This baby was on boiled milk feedings. A little catechizing brought out the fact that although the baby's diet list called for orange juice, it had been omitted.

The appearance of her gums discounted the automobile story, and her rapid improvement on orange juice confirmed the diagnosis of scurvy.

Lowenburg[1] reports the case of a baby with subperiosteal edema of the right thigh, submitted to the staff of a large chil-

[1] Lowenburg: Infant Feeding and Allied Topics, F. A. Davis Co., 1916, p. 228.

dren's clinic for an opinion. The following diagnoses were received: Sarcoma, rheumatism, osteomyelitis, periostitis, tuberculosis, rickets, and ununited fracture. A similar case shown to a group of fourth year students of a New York medical school brought forth almost identical suggestions.

Quite probably many babies with irritability and pallor are receiving too little vitamin C, and suffering from the unsuspected epiphyseal changes of scurvy without the fully developed picture of the disease.

Scurvy is too frequently an after-thought.

A nine-month-old baby who had done fairly well until six months of age was reported to have developed a coughing spasm during bronchitis, with

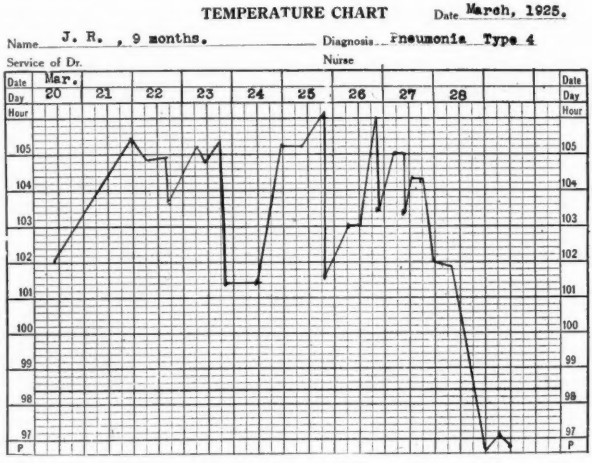

Fig. 122.—Uneventful pneumonia in a convulsion case receiving tetany treatment.

culmination of the attack in three convulsions associated with fever of 103 F. Two weeks later he had three more convulsions with fever, and six weeks later a third series of three convulsions during a bronchitis attack. His last convulsions had occurred eleven days before he came under observation. On physical examination he showed a bad nasopharyngitis and coughed in a manner suggesting whooping cough or laryngospasm, at times becoming quite cyanotic. Signs of general bronchitis were present. Although there were no blood chemistry observations, a justifiable guess is that this baby was in a state of latent tetany.

Cod liver oil was ordered and, in addition, 8 grains of calcium chloride four times daily.

This treatment was in effect only about four days before the baby developed a frank pneumonia, Type IV, with a temperature course shown by the accompanying chart (Fig. 122).

At no time, in spite of the superimposed infection, did the convulsions recur.

As a general rule when the opportunity of knowing the blood calcium content is lacking, it is a safe rule to assume the existence of so-called "latent tetany" in any infant who is extremely restless without discoverable cause, or on slight provocation has convulsions. In fact the existence of unrecognized tetany is so common that this condition should never be remote from the pediatrician's thought. Reassurance contributed by a negative Chvostek sign has little justification when blood calcium content is unknown.

For a quick cure of tetany one may today combine three agents: Calcium chloride or lactate, viosterol, and the ultraviolet ray.

A girl in the second year of life, who had had convulsions on two previous occasions, suddenly went into convulsions at about 8 A. M., and in spite of chloroform inhalations, and the administration internally of bromide and chloral, continued in active seizures for a period of more than four hours. Lumbar puncture yielded perfectly clear fluid not under increased pressure. Its sugar content was not determined.

Upon the advice of a consultant 1/16 grain of morphine was finally given hypodermically. This was apparently the most effective agent used in the case, for the child then went to sleep and her convulsions did not recur.

Nevertheless a period of hysterical screaming and insomnia followed, persisting with quiet intervals of variable duration, for more than a week. The condition called for the advice of a neurologist, and upon his suggestion a five-day period of starvation was instituted on the theory that the patient might be suffering from a type of toxemia that might be favorably influenced by withholding food. Gradually during this régime the irritability wore off with no persisting ill effects.

In some respects the case was strongly suggestive of encephalitis.

On another occasion when no adequate or permanent effects from chloroform were obtained in the case of a boy slightly over a year of age, who had previously had convulsions, and whose convulsions in this instance ushered in a tonsillitis attack, 1/24 grain of morphine was given hypodermically. Three hours after receiving the dose the child was sleeping peacefully with moderately slow respirations and extremely contracted pupils, but no untoward drug effects.

In all probability, morphine, although capable of serious toxic effects, should be used more frequently and with less delay than is customary in the persistent convulsion attacks of childhood. A single dose ranging from $\frac{1}{32}$ to $\frac{1}{24}$ grain is suggested, with the provision that atropine in dosage of $\frac{1}{300}$ to $\frac{1}{200}$ grain be given hypodermically if there are untoward effects from the morphine.

A girl about a year old had convulsions with tonsillitis, the seizures recurring with almost mathematical precision if temperature reached 104 F. A consultant in this instance said, "Keep the fever down." With more thorough antipyretic measures including plenty of aspirin the convulsions ceased.

In the case of a twelve-month-old boy with pneumonia the repeated and prolonged application of lukewarm wet towel packs combined with administration of 2½ grains of aspirin every two or three hours when the body temperature was over 104 F. apparently did much to allay the severe effects of the infection. In the intervals free from hyperpyrexia, this baby was comparatively free from dyspnea, and appeared only moderately ill. When treatment was omitted for several hours, fever rose to over 105 F., and prostration was again apparent.

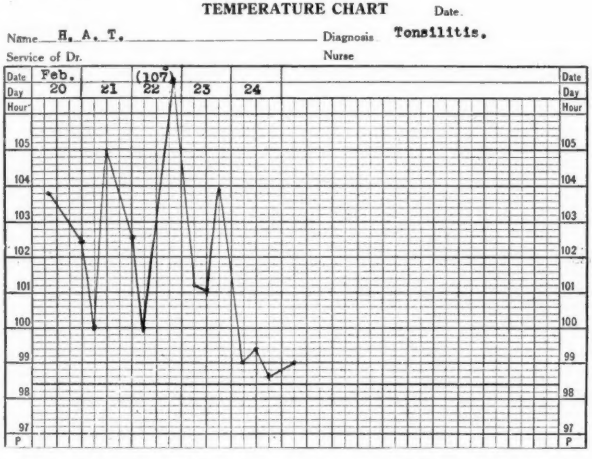

Fig. 123.—Characteristic hyperpyrexia of tonsillitis in a boy of six years.

The tendency of tonsillitis to cause high fever is exemplified by the chart shown in Fig. 123.

A continuous wet towel pack, not applied cold, and a moderate

dose of morphine hypodermically may be invaluable in the unusually persistent febrile convulsion case. Before the age of two years, between attacks, heliotherapy, calcium salts, and viosterol should be given a thorough trial.

While we appreciate that severe convulsive seizures may mean nothing worse than worms, indigestion during dentition, earache or tetany, we are too often forgetful that intracranial pathology may exist for days unrecognized because of a lack of neurologic manifestations. Particularly is this true of the young infant. Young children vomit so frequently from other causes that vomiting in infancy due to meningeal involvement is often wrongly interpreted.

The newborn infant, even when profoundly septic, may have no fever and no leukocytosis. *The infant with meningitis may present nothing to suggest the disease but bulging of the fontanel, and even this sign may be absent.*

A boy about twenty months old vomited with the onset of fever which rose quickly to 104 F. When seen at 5.30 P. M. soon after the onset, he appeared extremely toxic quite strongly suggesting pneumonia without lung signs. At 9.30 next morning after a very restless night he appeared generally no better, and his skin surface as a whole presented flea-bite-sized spots distributed about as closely as the usual chickenpox lesions. On close examination, the spots proved to be petechial. His conjunctivae also showed petechiae. With the exception of vomiting, there were no outstanding neurologic symptoms or signs.

Within eighteen hours following the first visit the child was taken to a hospital. His spinal fluid was found to be purulent, containing meningococcus, and his blood culture proved positive for meningococcus. His subsequent ear abscesses showed meningococcus.

After temporary improvement for about ten days under serum treatment, he died of pneumonia following a mastoid operation. Someone reported doing a lung puncture postmortem in lieu of an autopsy which was refused, and aspirating meningococcus from lung tissue. (This last finding was not positively confirmed.)

Contrast the case of a little girl of six years who developed a discharge from the left ear after two days of restlessness, ran an irregular fever for about ten days with no observed indications for paracentesis to secure better ear drainage, had a lower fever under 101.5 F. for two days and then vomited, developed diarrhea, became extremely irritable, complained of headache and finally exhibited strabismus, slowness in pupillary responses and slight stiff-

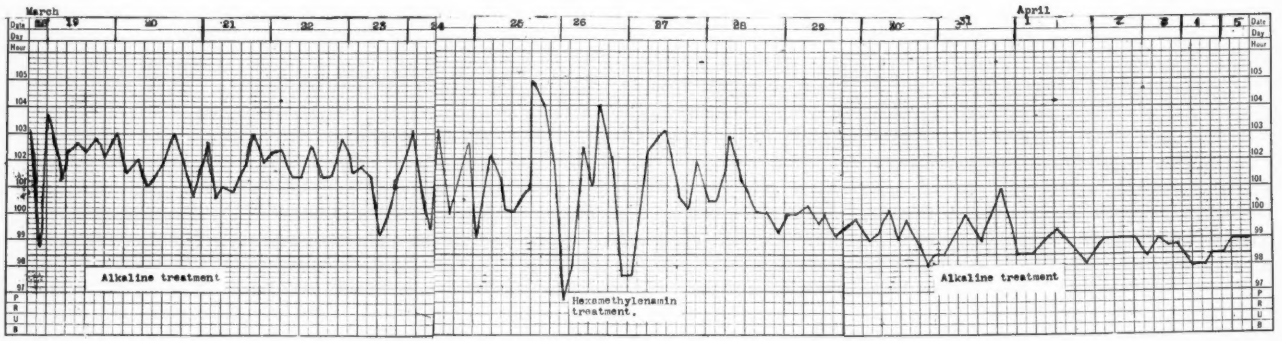

Fig. 124.—Typical pyelitis in Eleanor D., eight months old.

ness of the neck. Spinal fluid was found under extreme pressure and markedly cloudy with a cell count of 6000.

Antimeningococcus serum was given routinely from the time of the first spinal tap although blood culture and spinal fluid repeatedly were negative for organisms.

About three days after admission to the hospital, in view of the history and continued unfavorable course of the case, the left mastoid was operated upon. It was found deeply involved, but without evidence of sinus involvement or brain abscess. The patient then recovered.

Although this case may have been one of meningococcus meningitis with complicating mastoiditis, the interpretation of the otologists and of a consultant of wide experience with meningitis was that a sympathetic sterile type of meningitis had been induced by the ear condition. Serous meningitis of such a type would not have caused surprise, but what looked like a suppurative meningitis with a high cell count and no organisms in the spinal fluid, clearing up with mastoid drainage and serum administration, and called sympathetic meningitis, was most unexpected.

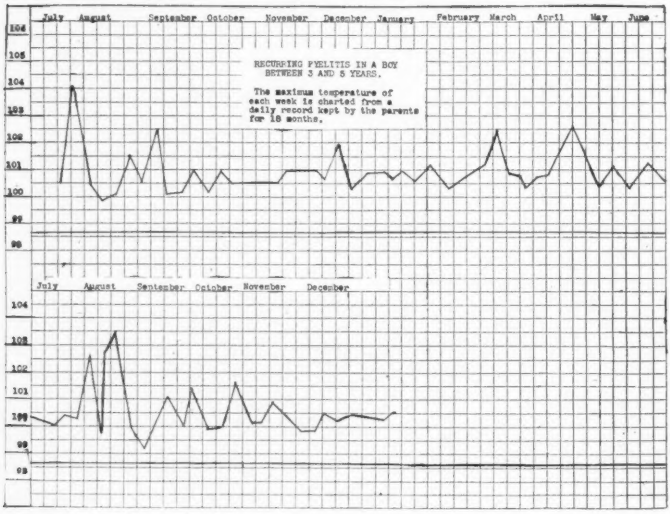
July August September October November December January February March April May June
RECURRING PYELITIS IN A BOY BETWEEN 3 AND 5 YEARS.
The maximum temperature of each week is charted from a daily record kept by the parents for 18 months.
July August September October November December
104
103
102
101
100
99
98

Fig. 125.—Acute exacerbations of chronic pyelitis during one and a half years.

On inquiry one readily finds that so-called *"aseptic" or sterile "sympathetic meningitis" is not extremely rare in association with severe otitis and mastoiditis.*

An object lesson of apparent value in prognosis is afforded by the accompanying charts of pyelitis cases (Figs. 124–127).

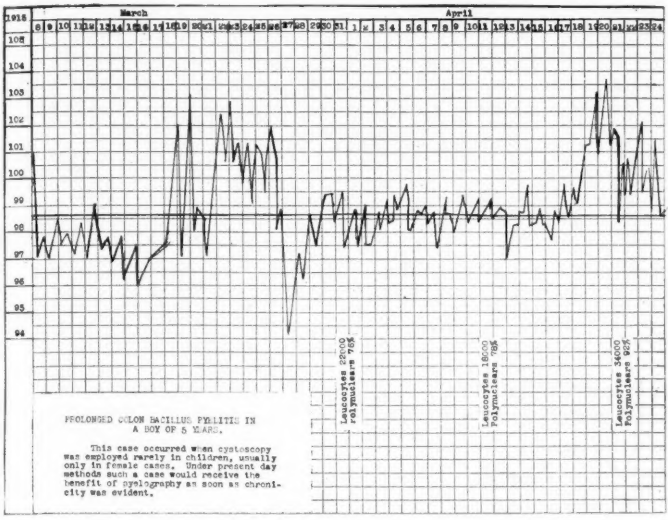
1918
March
April
PROLONGED COLON BACILLUS PYELITIS IN A BOY OF 5 YEARS.
This case occurred when cystoscopy was employed rarely in children, usually only in female cases. Under present day methods such a case would receive the benefit of cystography as soon as chronicity was evident.
Leucocytes 22000 Polymuclears 76%
Leucocytes 18000 Polymuclears 79%
Leucocytes 34000 Polymuclears 90%

Fig. 126.—Chronic pyelitis in a boy of five years.

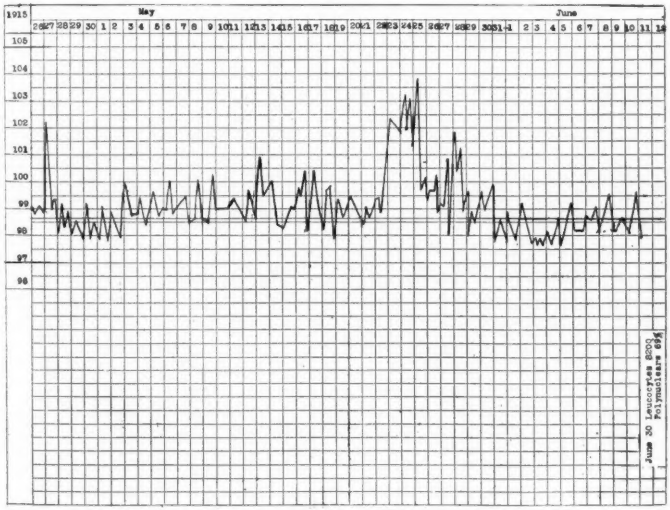

Fig. 127.—Chart of Fig. 126 continued.

A seven-month-old girl had been ill for over a week with vomiting and green stools. The mother insisted that the baby at the onset of the illness had a fever of 108 F., and that this observation was confirmed by a physician. On the following day the temperature had been as high as 105 F., but since for a few days the baby seemed improving, the doctor had not seen her, but had been receiving reports by telephone(!)

This baby, who at the end of the week of medical inactivity looked dehydrated enough for a clysis, and who was taking barley water with only a little milk, to prevent a recurrence of vomiting, kept down a weak evaporated milk mixture, absorbed a moderate amount of fluid by bowel, and rapidly improved.

Two days later the mother submitted a specimen of urine which she had been instructed to collect in a paper drinking cup with one side clipped out, and incidentally gave confirmation to the story of hyperpyrexia. The urine was loaded with pus.

Until comparatively recently special urological technic has not been employed in attacking chronic kidney infection in very young children. The characteristic chronicity of exceptional cases which today would call for cystoscopy and pyelography is exemplified in accompanying charts.

Figure 125 shows the record of a boy from three to four years of age whose parents had kept a diary of his temperature for one and a half years. On ordinary medical treatment when he came under observation at the end of this period, his pyuria rapidly cleared and he passed from observation after a few visits apparently well. That he had no recurrences later, however, seems doubtful.

Figures 126 and 127 show only a portion of the prolonged febrile course of chronic pyelitis in a boy of six years whose condition existed for many weeks unrecognized before he came under observation. Since his initial illness this boy has completed fifteen years of growth and development with only casual medical attention, and promises adult life of fair efficiency in spite of the fact that his kidneys are probably impaired.

Another boy about ten years old, whose urine was observed almost accidentally to contain pus and who excreted pus for months without being ill enough to run fever, lose weight, or miss school, was found after undergoing a bladder operation for the removal of a calcareous plaque, to require a nephrectomy. His left kidney was found to be tuberculous, the colon bacillus pyelitis picture having been superimposed upon the tuberculous kidney pathology.

Long-standing cases of pyelitis of this type are too frequently unsuspected of underlying tuberculosis.

Recently Dr. Meredith F. Campbell[1] has reported observations made in long-standing cases of pyelitis, including those of some very young infants. His work with that of other observers proves that much chronic pyelitis is due to anomalies in the urinary tract, and indicates that every case of prolonged pyelitis, even in infancy, deserves cystoscopic and *x*-ray work not only to complete diagnosis, but to give opportunity for permanent cure by relief of obstructions from whatever cause. In this connection, the studies of Campbell and Lyttle,[2] Wilson and Schloss[3] and others have indicated that the term "pyelitis" is actually a misnomer and that nephritis of some degree is present in all cases.

In reviewing object lessons of pediatrics, one should at least take cognizance of the thymus. Many authorities still believe that the thymus has something to do with cases of otherwise unexplained sudden death, whether with or without evidences of general status lymphaticus. Whether a small thymus like some small thyroids may be a mischief-maker without appealing to the roentgenologist as important probably depends on whether or not the thymus actually has an internal secretion. Certainly all large thymus glands are not productive of untoward symptoms. However, if a baby without tetany has attacks of suffocation, breath holding, rage spasms, or unexplained convulsions, few authorities would object to his having a few *x*-ray treatments without regard to the size of the "thymus shadow." Calcium salts and cod liver oil or viosterol might appropriately also be given.

In two fatal cases, symptoms such as one would ascribe to the thymus were explained by large heart shadows evidently due to congenital malformation of the heart. Only one of the babies had a fairly definite heart murmur.

[1] Campbell, M. F.: Amer. Jour. of Surg., November, 1928.

[2] Campbell, M. F., and Lyttle, J. D.: Ureteral Obstruction in Infancy: A Clinico-Pathologic Study of Seventy-four Cases, Jour. Amer. Med. Assoc., 92, 544, February 16, 1929.

[3] Wilson, J. R., and Schloss, O. M.: Pathology of So-called Acute Pyelitis in Infants, Amer. Jour. Dis. of Child., 38, 227, August, 1929.

Congenital heart malformation may simulate so-called "thymic dyspnea."

Object lessons from the cases of children beyond the period of infancy often emphasize mistakes in prognosis.

A boy, thirteen years old, who, in spite of early tonsillectomy, had had a subsequent history of throat infection and rheumatism, came under observation in midsummer with active choreic movements, including choreic speech and salivation. Under rest, codeine, and salicylate in dosage up to a total of 80 grains or more daily, he improved enough in two weeks to feed himself soup without mishap. His heart examination at this time detected only a doubtful, almost imperceptible systolic murmur in spite of his mother's report that he had previously been thought to have a definite lesion. However, a crop of subcutaneous nodules, noted chiefly in the aponeurosis of the scalp, suggested a thoroughly established infection.

For a time this case constituted an apparent exception to Brenneman's[1] rule that such nodules augur severe endocarditis, for through the remainder of the summer, fall, and winter following chorea, the boy remained well. Nevertheless, in April, nearly ten months after the chorea, he developed swelling of the ankles, pain in one wrist, a characteristic erythema, a low grade but obstinate fever (perhaps modified by salicylate, but not definitely controlled by the drug), and another outbreak of subcutaneous nodules. During this attack the heart developed a very audible, mitral regurgitant murmur and later a double mitral murmur.

Much to the discredit of the physicians in attendance, about the time the bad prognosis was disclosed to the family, the whole process subsided and after a quiet summer in the country, the boy was presented for examination, at the age of fourteen, with heart doing normal work and only a slight apical systolic murmur.

There was no recognized recurrence or exacerbation of infection up to the age of seventeen at which time the boy was last examined.

Another boy, eleven years old, who had had chorea twice and had been under the observation of a specialist for some uncertain cardiac condition, developed headache, fever, moderate stiffness of the neck and slight tonsillitis two weeks following a grip attack which occurred late in December. His gums were acutely inflamed and bled readily when rubbed. His throat was moderately inflamed. His pulse rate ranged from 80 to 90, and his fever from 100 to 101 F. His heart showed no enlargement, and the systolic murmur which was audible at the apex was so slight as to seem not definitely organic. It was indeed doubtful whether the boy had an active rheumatic infection until a few days had elapsed, when he displayed a crop of subcutaneous nodules with a localization chiefly occipital. About this time, although his mouth condition had been cleared up, endocarditis became definitely apparent.

[1] J. Brenneman: Amer. Jour. Dis. of Child., Sept., 1919.

In the case of the first boy, with the choreic history, a consultant gave a very bad prognosis. In the case of the second boy, a doctor, whose services the family terminated, was reported to have said he was glad to be "off the case" because the patient was not going to recover. Nevertheless, after a number of weeks in bed during which the nodules disappeared, and the heart tone improved, this boy was able to assume a fair amount of activity. Before the summer was ended he underwent tonsillectomy without difficulty. Now with no recurrence of rheumatism in seven years, he is planning to enter college. Although he has a mitral lesion, an ordinary life insurance examination without the history might miss the signs.

These cases are significant not because recoveries from endocarditis are unique, but because such exceptional instances show that *even the obstinate subcutaneous nodule type of rheumatism may let up its grip for a period long enough to give a supposed victim a chance to have another disease.*

If there were sufficient space one might attempt to prove clinically by object lessons that acidosis is a symptom-complex and not a disease although on this point many practitioners are probably already agreed. Justification in any event exists for the question whether in the cases of older children vomiting persistently, it is sensible to try to feed anything liquid in quantity, whether it is bicarbonate of soda water, Kalak water, Vichy, ginger ale, orange juice, or pineapple juice.

Such children need a nonirritant laxative such as milk of magnesia, a colon irrigation, a hypodermic injection of codeine or morphine, a mustard paste on the abdomen and a good rest, then some thick oatmeal paste with a little sugar, but no milk, and (if the cereal "stays down") an hour or two later some sips of hot tea and a piece of hard toast. No water except sips of hot water and no cracked ice should be permitted till this program has been completed and gastric tolerance is assured.

If the scheme fails, one may try the liquids and if necessary call the chemist and the transfusionist, but he should remember that before the child got acidosis probably he had a fever due to tonsillitis, somebody gave him a nauseating dose of castor oil, and then the whole family carried cold milk or ice cream to him because it tasted good and he refused simple carbohydrate food such as cereal gruel.

In spite of this, the case of the little fellow about three years old, who shopped all afternoon at the end of a long railroad trip, vomited for two days, and on the third day went into stupor, and died in a few hours almost before thorough-going treatment was instituted, makes one feel, on hearing of similar previous severe attacks in the same patient, that such a virulent type of chemical toxemia belongs in the category of primary diseases.

Some of the most striking lessons of pediatrics are enforced by cases of peculiar complexity calling for the breaking of those rules which are unquestionably applicable to one condition existing alone.

R. M., three years old, became ill with tonsillitis and whooping cough almost simultaneously, and then began to void bloody urine containing quantities of albumin, red cells, and casts. Whooping cough vaccine was administered without apparent effect on the course of the pertussis. With the gradual subsidence of the cough, the problem of tonsillectomy, which could not be considered at the outset of the case, was presented as a paramount issue because of the belief that the persisting hemorrhagic nephritis was due to tonsil infection. Unfortunately, the few days of normal temperature desired before tonsillectomy could safely be performed did not materialize, owing to the development of an abscess in the deep cervical gland chain subjacent to the left sternomastoid. After the abscess had been opened and drained, there was an apparent recurrence of tonsil infection and with no improvement in the nephritis and increasing depletion of the patient's strength, it became evident that a radical course was necessary (Fig. 128).

Tonsillectomy was performed by Dr. Frank C. Keil at a time when the little patient's temperature was 101.8 F., his hemoglobin 44 per cent, his red cells were 2,876,000, his leukocytes 24,000, his polynucleas 82 per cent, and his urine contained albumin, a considerable number of red cells, and hyaline casts. At operation a pus cavity was unexpectedly encountered deep under the left tonsil, closely contiguous to, but not definitely continuous with the cervical abscess. With evacuation of this pus collection and renewal of drainage from the neck wound, the patient's temperature quickly subsided, and within a week the nephritis picture had completely changed for the better.

During the two and a half years' interval since operation, this child has been practically well with no residua of his prolonged illness except a slight intermittent albuminuria.

Although tonsillectomy in acute illness is contraindicated, it is justifiable to relie on even incomplete barriers around an infection when the patient's life is at stake.

At noon of July 26th an eighteen-month-old boy was seen by his mother to swallow an open safety pin. The patient was immediately brought to

the hospital and submitted to *x*-ray within four hours of the time of the accident. The first film was not good because of the child's movements and a second was taken on the next day showing the region comprising the alimentary tract from suprasternal fossa to anus. This film was examined by a number of observers. As no pin was shown the patient was discharged from the hospital apparently well two days after admission, July 28th.

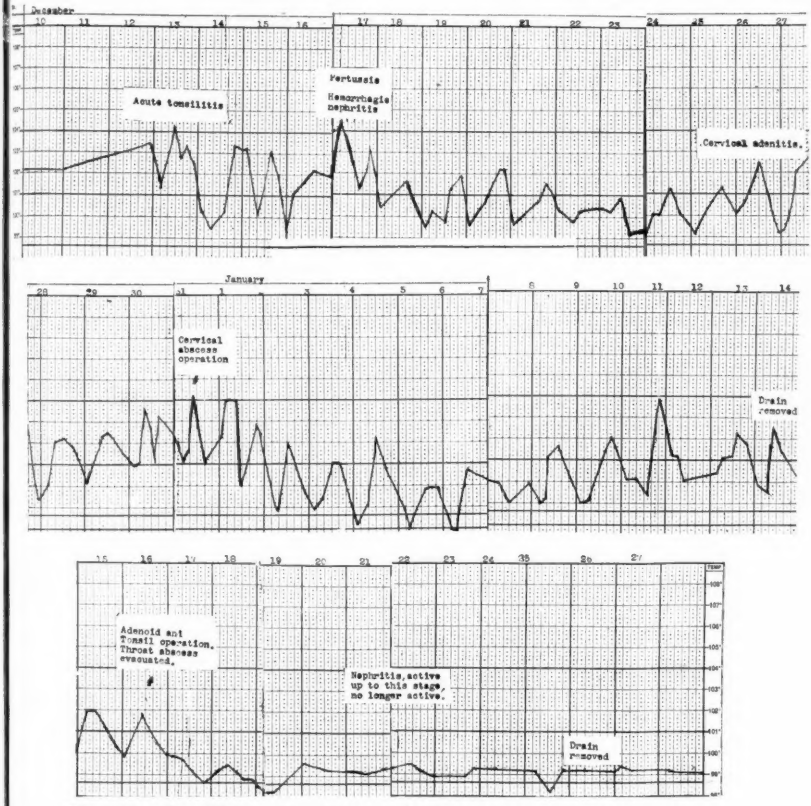

Fig. 128.—Tonsillitis, pertussis, hemorrhagic nephritis, cervical gland abscess, subtonsillar abscess. Tonsillectomy and drainage during acute stage.

On August 4th the child was again brought for examination, his mother stating that, although there had been no vomiting, diarrhea, or fever, the baby would not take his food well and acted as if, in spite of the negative evidence of the *x*-ray, the pin might really be troubling him.

The baby was given castor oil and denied milk for twelve hours; then given a diet limited to cereals, vegetables, and skim milk. About two days later the mother reported by telephone that the child was no better, and was advised to call a physician in her neighborhood. She later reported that his findings were practically negative, but that the patient really did not seem well for a space of ten days.

Gradually appetite and color improved, activity was resumed, and the good health characteristic before the incident of July 26th was continued with a gain in weight of $2\frac{1}{2}$ pounds.

On the morning of October 13th, two and a half months after the accident, without premonitory signs of pain or other symptoms, the child expelled an open safety pin with the act of defecation, and this the mother contended was positively the same pin swallowed on July 26th.

The explanation of failure of the *x*-ray to reveal the foreign body was made easy by the belated discovery that the view had been taken too low to show the level of the cricoid cartilage, a most frequent stopping place for swallowed articles.

Truly one may not only infer, but conclude, that the principal thing in clinical pediatrics is to receive the object lesson from the case.